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OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

THIRTY-FOURTH SESSION

HELD AT ATLANTIC CITY, N. J.

JUNE 16, 17 AND 18, 1919

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NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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ALTERNATE REPRESENTATIVE

FRANCIS W. PEABODY, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis A. Delafield	.....	.....	James Tyson.	A. B. Ball
1887.	S. Weir Mitchell.	Francis Minot. / R. Palmer Howard.	J. T. Whittaker.	G. L. Peabody.	W. W. Johnston
1888.	Wm. H. Draper.	Francis Minot. / R. Palmer Howard	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. / S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. / Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1916.	Henry Sewall.	George Dock.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1917.	George Dock.	F. H. Williams.	T. R. Boggs.	T. McCrae.	J. P. C. Griffith.
1918.	F. H. Williams.	Alex. McPhedran.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.
1919.	Alex. McPhedran.	Herman M. Biggs.	W. W. Ford.	T. McCrae.	Joseph A. Capps.
1920.	H. M. Biggs.	W. S. Thayer.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.

ACTIVE MEMBERS

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Johns Hopkins Medical School, Baltimore, Md.
1894. Adami, J. George, Univ. of Liverpool, Liverpool, England.
1905. Adams, Samuel S., 1801 Connecticut Ave., Washington, D. C.
1919. Addis, Thomas, Lane Hospital, San Francisco.
1918. Allen, F. M., Rockefeller Institute, 66th St. and Ave. A., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1913. Anderson, John F., 195 College Ave., New Brunswick, N. J.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1913. Auer, John, Rockefeller Institute, 66th St. and Ave. A, New York.
1919. Austin, J. H., Rockefeller Institute, 66th St. and Ave. A, New York.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1916. Bass, Charles C., Tulane Univ., New Orleans.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 122 S. Michigan Blvd., Chicago.
1901. Blumer, George, 204 York St., New Haven, Conn.
1913. Boggs, Thomas R., 21 West Chase St., Baltimore, Md.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1915. Brill, Nathan E., 48 W. 76th St., New York.
1913. Brooks, Harlow, 5 West 9th St., New York.
1911. Brown, Lawrason, 104 Main St., Saranac Lake, N. Y.
1904. Brown, Philip K., 516 Sutter St., San Francisco, Cal.
1914. Brown, Thomas R., 19 W. Biddle St., Baltimore.
1918. Brown, W. H., Rockefeller Institute, 66th St. and Ave. A, New York.
1913. Bunting, C. H., University of Wisconsin, Madison.
1899. Cabot, R. C., 1 Marlborough St., Boston.
1912. Camac, C. N. B., 128 E. 60th St., New York.
1914. Cannon, Walter B., Harvard Medical School, Boston.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1919. Carter, E. P., 204 Stratford Road, Guilford, Baltimore.
1907. Christian, Henry A., 252 Marlborough St., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.

ELECTED

1917. Cohn, Alfred E., 315 Central Park West, New York.
1909. Cole, Rufus I., 960 Park Ave., New York.
1914. Coleman, Warren, 58 West 55th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1917. Dochez, Alphonse R., Rockefeller Institute, 66th St. and Ave. A, New York.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1915. Emerson, Charles P., Medical School, University of Indiana, Indianapolis.
1918. Emerson, Haven, 120 E. 62d St., New York.
1915. Erlanger, Joseph, 600 S. Kingshighway, St. Louis.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1916. Foster, Nellis B., University Hospital, Ann Arbor, Mich.
1908. Freeman, R. G., 211 W. 57th St., New York.
1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1917. Frothingham, Jr., Channing, 395 Marlborough St., Boston.
1918. Fulton, F. T., 273 Bowen St., Providence, R. I.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 23 West Franklin St., Baltimore.
1914. Gay, Frederick P., University of California, Berkeley.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer. 1810 Spruce St., Philadelphia.
1919. Hamburger, W. W., 104 S. Michigan Ave., Chicago.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1915. Hamman, Louis V., 714 Park Ave., Baltimore.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1918. Hart, T. S., 160 W. 59th St., New York.
1918. Heard, J. D., 6101 Penn Ave., Pittsburgh, Pa.
1898. Herrick, James B., People's Gas Building, Chicago.
1910. Hewlett, Albion W., Stanford Med. School, San Francisco, Cal.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
1916. Hunt, J. Ramsay, 20 W. 50th St., New York.

ELECTED

1907. Hunt, Reid, Harvard Med. School, Boston.
1917. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1916. Jobling, James W., Dept. of Pathology, Columbia Univ., New York.
1902. Joslin, E. P., 81 Bay State Road, Boston.
1916. Karsner, Howard T., Lakeside Hospital, Cleveland.
1915. Klotz, Oskar, University of Pittsburgh, Pittsburgh.
1900. Koplik, Henry, 30 East 62d St., New York.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 11 S. 21st St., Philadelphia.
1917. Lee, Roger I., Harvard Medical School, Boston.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, 600 S. Kingshighway, St. Louis.
1909. Longcope, Warfield T., 41 E. 70th St., New York.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1919. McLean, F. C., Peking Union Medical College, 61 Broadway, New York.
1919. McLester, J. S., Empire Building, Birmingham, Ala.
1891. McPhedran, A., 151 Bloor St. W., Toronto, Canada.
1902. MacCallum, W. G., The Hopkins Hospital, Baltimore.
1905. Macallum, A. B., Ottawa, Canada.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1919. Meakins, J. C., Dept. of Therapeutics, Edinburgh Univ., Edinburgh, Scotland.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
1917. Miller, James A., 379 Park Ave., New York.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1915. Morris, Roger S., Cincinnati General Hospital, Cincinnati.
1917. Mosenthal, Herman O., 49 E. 53rd St., New York.
1919. Newburgh, L. N., Univ. Hospital, Ann Arbor, Mich.
1915. Noguchi, Hideyo, Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Norris, Geo. W., 1530 Locust Street, Philadelphia.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1918. Ordway, T., Albany Medical College, Albany, N. Y.
1919. Palmer, W. W., The Hopkins Hospital, Baltimore.
1899. Park, Wm. H., 315 West 76th St., New York.

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1904. Pearce, R. M., Rockefeller Foundation, 61 Broadway, New York.
1918. Piersol, George Morris, 1913 Spruce St., Philadelphia, Pa.
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1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1899. Prince, Morton, 458 Beacon St., Boston.
1894. Rachford, B. K., 1961 Madison Rd., Cincinnati.
1904. Richardson, Mark W., 67 Milk St., Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1915. Robinson, G. Canby, 600 S. Kingshighway, St. Louis.
1907. Rosenau, M. J., Harvard Medical School, Boston, Mass.
1916. Rous, Peyton, 131 E. 19th St., New York.
1915. Rowntree, Leonard G., Univ. of Minn., Minneapolis.
1911. Rudolf, Robert D., 100 College Ave. W., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 116 W. 59th St., New York.
1908. Sailer, Joseph, 1718 Spruce St., Philadelphia.
1919. Sellards, A. W., Harvard Med. School, Boston.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1892. Smith, Theobald B., Princeton, N. J.
1907. Sollmann, Torald H., 1353 E. 9th St., Cleveland, Ohio.
1916. Steiner, Walter R., 646 Asylum Ave., Hartford, Conn.
1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, R. P., Harvard Medical School, Boston.
1917. Swift, Homer F., 65 Central Park West, New York.
1916. Taussig, Albert E., Metropolitan Bldg., St. Louis.
1907. Taylor, A. E., University of Pennsylvania, Philadelphia.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 61 W. 49th St., New York.
1912. Tileston, Wilder, 424 Temple St., New Haven.
1914. Wadsworth, Aug. B., 278 Yates St., Albany.
1901. Warthin, Aldred S., Univ. of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.
1918. Webb, G. B., Colorado Springs, Colo.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1913. Whipple, Geo. H., Hooper Foundation, University of California Hospital, San Francisco, California.
1917. White, Franklin W., 322 Marlborough St., Boston.
1918. White, S. M., Donaldson Bldg., Minneapolis, Minn.

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1915. White, Wm. Charles, 2851 Bedford Ave., Pittsburgh.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1918. Wolbach, S. B., Harvard Medical School, Boston, Mass.
1917. Wood, Edward J., 201 Chestnut St., Wilmington, N. C.
1914. Wood, Francis C., 437 W. 59th St., New York.
1916. Woodyatt, Rollin T., 104 S. Michigan Ave., Chicago.

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1918. Draper, G., 116 E. 63d St., New York.
1916. Edmunds, Charles W., Univ. of Michigan, Ann Arbor, Mich.
1915. Einhorn, Max, 20 E. 63d St., New York.
1918. Evans, J. S., University of Wisconsin, Madison, Wis.
1916. Eyster, John H., Univ. of Wisconsin, Madison, Wis.
1918. Fitz, R., Rockefeller Institute, 66th St. and Ave. A, New York.
1919. Funk, E. H., 1318 Spruce St., Philadelphia.
1918. Giffin, H. Z., Mayo Clinic, Rochester, Minn.
1917. Hess, A. F., 16 W. 86th St., New York.
1916. Hirschfelder, Arthur D., Univ. of Minnesota, Minneapolis.
1917. Krumbhaar, E. B., Med. Dept., Univ. of Pa., Philadelphia.
1917. Lewis, P. A., Phipps Institute, Philadephia, Pa.
1916. Loevenhart, Arthur S., Univ. of Wisconsin, Madison, Wis.
1919. Means, J. H., 15 Chestnut St., Boston.
1919. Minot, G. S., 188 Marlborough St., Boston.
1919. Murphy, J. B., Rockefeller Institute, 66th St. and Ave. A, New York.
1918. Musser, John H., 338 S. 21st St., Philadelphia, Pa.
1918. Rehfuss, M. E., 16th and Spruce Sts., Philadelphia, Pa.
1916. Rosenow, Edward C., Mayo Clinic, Rochester, Minn.
1916. Shattuck, George C., 135 Marlborough St., Boston.
1919. Walker, J. C., Peter Bent Brigham Hospital, Boston.
1917. Warfield, L. M., 79 Wisconsin St., Milwaukee.

HONORARY MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED HONORARY MEMBER	
	1916.	Gorgas, William C., Surgeon-General, U. S. A., Washington, D. C.
*1886.	1915.	Hun, Henry, 149 Washington Ave., Albany.
1902.	1916.	Kober, Geo. M., 1819 Q St., N. W., Washington.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York.
1889.	1915.	Vaughan, Victor C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore.

EMERITUS MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1905.	1918.	Babcock, R. H., 74 East Elm St., Chicago.
1908.	1919.	Baldwin, E. R., Saranac Lake, New York.
1898.	1916.	Blackader, A. D., 236 Mountain St., Montreal.
1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1898.	1917.	Brannan, John W., 48 W. 51st St., New York.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of Edinburgh, Edinburgh, Scotland.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1901.	1919.	Edwards, A. R., 104 S. Michigan Ave., Chicago.
1888.	1919.	Ernst, H. C., 8 Greenough Ave., Jamaica Plain, Mass.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
1900.	1917.	Holt, L. E., 14 W. 55th St., New York.
1890.	1902.	Hurd, H. M. Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1895.	1918.	Lafleur, H. A., 215 Peel St., Montreal, Canada.
1888.	1919.	Lewis, M. J., 1316 Locust St., Philadelphia.
1898.	1916.	Mallory, F. B., Harvard Medical School, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1891.	1918.	Northrup, W. P., 61 E. 73d St., New York.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
1903.	1918.	Preble, R. B., 590 Dearborn Ave., Chicago.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street. Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
1899.	1918.	Thacher, J. S., 20 W. 50th St., New York.
1898.	1918.	Vickery, H. F., Ipswich, Mass.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

1896. Adler, Isaac, New York.
*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
*1886. Henry, F. P., Philadelphia.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.

DATE OF ELECTION

*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
1908. Janeway, T. C., Baltimore.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1901. Kinyoun, J. J., Washington.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
*1886. McBride, Thomas A., New York.
1914. McCrae, John, Montreal, Canada.
1890. MacDonnell, R. P., Montreal, Canada.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1898. Mitchell, John K., Philadelphia.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
*1886. Putnam, James J., Boston.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.

DATE OF ELECTION

1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
1889. Thomson, W. H., New York.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Tyson, James, Philadelphia.
*1886. Ward, Samuel B., Albany.
1898. Wesbrook, F. F., Vancouver.
*1886. Whittaker, James T., Cincinnati.
*1886. Wilkins, George, Montreal.
1898. Withington, Charles F., Boston.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended June 17, 1919

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to two hundred. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of Emeritus members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the

Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, twenty-five shall be necessary for a quorum, and for altering the Constitution fifty members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the

nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such as the Council from time to time may fix, from the payment of which honorary and emeritus members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-FOURTH ANNUAL MEETING

Held at the Hotel Traymore, Atlantic City, N. J., June 16, 17 *and* 18, 1919

The following members were present at the meeting:

Abbott, A. C.
Adams, Samuel S.
Addis, T.
Anders, James M.
Anderson, John F.
Babcock, R. H.
Barker, L. F.
Bass, Charles C.
Biggs, Herman M.
Billings, Frank
Bond, Charles S.
Brill, Nathan E.
Brown, Lawrason
Cabot, R. C.
Camac, C. N. B.
Capps, Joseph A.
Christian, Henry A.
Cohen, Solomon Solis
Cohn, Alfred E.
Cole, Rufus I.
Collins, Joseph
Conner, Lewis A.
Coplin, W. M. L.
Dochez, Alphonse R.
Dock, George
Edsall, David L.
Erlanger, Joseph
Ernst, Harold C.
Ewing, James
Fitz, R.
Flexner, Simon
Ford, W. W.
Freeman, R. G.
Friedenwald, Julius
Frothingham, C., Jr.
Fulton, F. T.
Fussell, M. Howard
Futcher, Thomas B.
Gay, Frederick P.
Giffin, H. Z.
Griffith, J. P. Crozer
Hamburger, W. W.
Hamilton, W. F.
Hamman, Louis V.
Hare, Hobart A.
Hart, T. S.
Heard, J. D.
Herrick, James B.
Hirschfelder, A. D.
Hoover, C. F.
Howard, Campbell P.
Hunt, J. Ramsay
Irons, Ernest E.
Jackson, Henry
Joslin, E. P.
Klotz, Oskar
Kober, G. M.
Koplik, Henry
Krumbhaar, E. B.
Landis, H. R. M.
Lee, Roger I.
Lewis, P. A.
Libman, E.
Locke, Edwin A.
Loeb, Leo
Longcope, Warfield T.
Lord, Frederick T.
McCrae, Thomas
McPhedran, A.
MacCallum, W. G.
Meakins, J. C.
Meltzer, S. J.
Meyer, Adolph
Miller, James A.
Miller, Joseph L.
Mosenthal, Herman O.
Musser, J. H., Jr.
Newburgh, L. N.
Noguchi, Hideyo
Norris, George W.
Novy, F. G.
Ordway, T.
Peabody, Francis W.
Pearce, R. M.
Piersol, George Morris
Plummer, H. S.
Pratt, Joseph H.
Preble, R. B.
Prince, Morton
Rachford, B. K.
Riesman, David
Robinson, G. Canby
Rosenau, M. J.
Rosenow, E. C.
Russell, Frederick F.
Sailer, Joseph
Sewall, Henry
Shattuck, G. C.
Southard, Elmer E.
Steiner, Walter R.
Stengel, Alfred
Stockton, Charles G.
Swift, Homer F.
Thayer, W. S.
Tileston, Wilder
Wadsworth, Aug. B.
Warfield, L. M.
Warthin, Aldred S.
Webb, G. B.
White, S. M.
Williams, Herbert U.
Wilson, Louis B.
Wood, Edward J.

Monday, June 16

The Association was called to order by President McPhedran at 9 A.M., who then delivered the President's address.

The Treasurer presented his report showing a balance of $803.96. The President appointed Drs. Futcher and Lord to act as an Auditing Committee.

The Secretary presented the report of the Council:

1. That the dues for the coming year be the same as for the previous year and that full-time clinical workers who have no professional income apart from their salaries should pay the same fee as full-time laboratory workers.

2. Regarding the proposed amendments to the Constitution, the Council suggested that the first amendment be changed to read 200 in place of 250, and if this be adopted that it be an instruction to the Council that not more than 5 of the new places be filled in any one year. The adoption of the second amendment abolishing the class of Associate Members was advised against. The adoption of the amendment that "membership shall be forfeited unless some meritorious contribution to medicine be published at least once in every three years" was advised against.

The change in the numbers required for a quorum from 15 to 25 for the election of members and 25 to 50 for the adoption of amendments to the Constitution was advised for adoption.

3. The list of nominations, as given elsewhere, for officers and new members.

The program was then proceeded with:

Dr. E. E. Southard presented a paper on the "Elements of a Pragmatic Psychiatry" and Dr. J. Collins on the "Imminent Psychology: A Plea and a Prophecy," which were discussed by Drs. R. C. Cabot, Frederick P. Gay, Adolph Meyer, and the discussion closed by Dr. Southard.

Dr. L. F. Barker presented a paper on "Epidemic Encephalitis," which was discussed by Drs. E. Libman, J. Collins, Frank Billings, M. Howard Fussell, and the discussion closed by Dr. Barker.

Dr. C. Frothingham presented a paper on "The Diagnosis of Syphilis of the Central Nervous System," which was discussed by Drs. J. Collins M. J. Rosenau and Homer F. Swift.

Dr. G. Dock presented a paper on "Some Findings in 3000 Consecutive Medical Cases with Wassermann Examination," which was discussed by Dr. H. Noguchi.

Dr. H. Z. Giffin presented a paper on "Eosinophilic Polymorphonuclear Leukemia," which was discussed by Drs. L. F. Barker, E. Libman, A. S. Warthin, Francis W. Peabody, E. B. Krumbhaar, Joseph A. Capps, and the discussion closed by Dr. Giffin.

Dr. G. G. Stockton presented a paper on "A Long Duration of Remission in Pernicious Anemia" and Dr. J. M. Anders presented a paper on "Transfusion of Blood in Pernicious Anemia: Report of an Interesting Case," which were discussed by Drs. J. L. Miller, G. Dock, T. B. Futcher, Frank Billings, J. Friedenwald, R. C. Cabot, E. Libman, and the discussion closed by Dr. Anders.

Dr. F. P. Gay presented a paper on "Experimental Streptococcus Empyema: The Possibilities of its Prevention and Cure by Specific Means," which was discussed by Dr. A. B. Wadsworth.

Dr. A. R. Dochez presented a paper on "Immunologic Relationships Between Strains of Streptococcus Hemolyticus."

Dr. W. W. Ford presented a paper on "An Antihemolysin for the Hemolysin of the Gas Bacillus," which was discussed by Dr. H. Noguchi and the discussion closed by Dr. Ford.

Dr. S. J. Meltzer presented a paper on "Functional Impermeability of the Cardia," which was discussed by Dr. H. S. Plummer.

Tuesday Morning, June 17

The following Officers and New Members were elected:

President—H. M. Biggs.

Vice-President—W. S. Thayer.

Secretary—Thomas McCrae.

Recorder—T. R. Boggs.

Treasurer—J. A. Capps.

Council—L. A. Conner.

Active Members—T. Addis, San Francisco; J. H. Austin, Philadelphia; E. P. Carter, Baltimore; W. W. Hamburger, Chicago; F. C. McLean, Pekin; J. S. McLester, Birmingham; J. C. Meakins, Montreal; L. N. Newburgh, Ann Arbor; W. W. Palmer, New York; A. W. Sellards, Boston.

Associate Members—R. Cecil, New York; E. H. Funk, Philadelphia; J. H. Means, Boston; G. S. Minot, Boston; J. B. Murphy, New York; I. C. Walker, Boston.

Amendments to the Constitution.

The suggestion of the Council that the number 200 be substituted for 250 in the first amendment was adopted and then the amendment as changed was adopted. This makes Article II read: "The number of Active Members shall be limited to two hundred." The Council was instructed not to fill more than five of these new places in any one year.

The amendment to omit the class of Associate Members was not adopted.

The amendment "Membership shall also be forfeited unless some

meritorious contribution to medicine be published at least once in three years" was not adopted.

The amendment changing the number necessary for a quorum for the election of members from fifteen to twenty-five and for altering the Constitution from twenty-five to fifty was adopted.

The Auditors reported that the Treasurer's accounts had been audited and found correct.

Dr. J. Friedenwald presented a paper on "A Case of Perforated Gastric Ulcer with Abscess Formation, Perforation through the Lung, with Spontaneous Recovery."

Dr. C. F. Hoover presented a paper on "How Partial Paralysis and Regional Paralysis of Intercostal Muscles Affect Lung Ventilation," which was discussed by Drs. S. J. Meltzer and L. A. Conner, and the discussion closed by Dr. Hoover.

Dr. G. Shattuck presented a paper on "Chest Wounds in War from the Medical Standpoint," which was discussed by Drs. H. Sewall, C. F. Hoover, S. J. Meltzer, Joseph Sailer, and the discussion closed by Dr. Shattuck.

Dr. F. T. Lord presented a paper on "Certain Factors Influencing Recovery from Pneumonia, with Special Reference to the Chemistry of the Exudate," which was discussed by Drs. E. Libman, C. F. Hoover, S. S. Cohen, and the discussion closed by Dr. Lord.

Drs. S. S. Cohen and G. D. Heist presented a paper on "A New Method for Testing Immunity by Means of the Whole Blood, with Especial Reference to Pneumonia and its Prophylaxis by Bacterination."

Dr. G. C. Robinson presented a paper on "The Rapidity and Persistence of the Action of Digitalis on the Heart," which was discussed by Drs. S. M. White, S. S. Cohen, L. A. Conner, J. Erlanger, and the discussion closed by Dr. Robinson.

Dr. L. M. Warfield presented a paper on "Observations on the Effort Syndrome among the Drafted Men at a Recruit Depot," which was discussed by Drs. J. D. Heard, J. C. Meakins, and the discussion closed by Dr. Warfield.

Dr. L. A. Conner presented a paper on "Cardiac Diagnosis in the Light of Experiences with Army Physical Examinations," which was discussed by Drs. S. S. Cohen, W. S. Thayer, Frank Billings, H. S. Plummer, Alfred Stengel, and the discussion closed by Dr. Conner.

Dr. H. Sewall presented a paper on "Observations on Certain Respiratory and Vasomotor Variations of Human Arterial Blood-pressure," which was discussed by Dr. J. Erlanger, and the discussion closed by Dr. Sewall.

Dr. E. Libman presented a paper on "Some Observations on Thrombosis of the Coronary Arteries."

Tuesday Evening, June 17

Drs. H. K. Pancoast and H. R. M. Landis presented a paper on "Fixation of the Diaphragm Following Inflammation of the Pleura."

Dr. Thomas McCrae presented a paper on "Physical Signs Associated with Foreign Bodies in the Bronchi," which was discussed by Drs. H. A. Hare and H. S. Plummer

Dr. W. G. MacCallum presented a paper on "Types of Pneumonia Following Influenza."

Dr. Simon Flexner presented a paper on "Lethargic Encephalitis."

Lt. Col. Hurst, of London, showed films demonstrating the results of treatment in war neuroses.

Drs. S. Gasser and J. Erlanger presented a paper on "Hypertonic Gum Acacia and Glucose in the Treatment of Secondary Traumatic Shock."

Dr. J. Meakins presented a paper on "The Significance of Prolongation of the Ventricular (Cardiac) Excitatory Process."

Dr. C. C. Bass presented a paper on "The Relative Frequency of Malaria in Persons of Different Ages and Age Groups in an Area of Great Prevalence."

Drs. L. Sampson and L. Brown presented a paper on "The Early Diagnosis of Intestinal Tuberculosis."

Dr. A. S. Warthin presented a paper on "Ayerza's Disease (Polycythemia with Syphilis of the Pulmonary Arteries)," which was discussed by Dr. E. Libman.

Dr. E. C. Rosenow presented a paper on "Animal Experiments with Bacteria Isolated from the Influenza and Pneumonia."

Dr. L. H. Newburg presented a paper on "The Production of Bright's Disease by Feeding High Protein Diets."

Drs. J. P. Peters and W. G. Longcope presented a paper on "A Study in War Nephritis (Urinary Tract Purpura): A Probable Entity."

Wednesday Morning, June 18

Dr. G. Kober presented a paper on "Dr. Osler's Influence on American Medicine."

On motion of Dr. Joslin, seconded by all present, the following resolution was adopted:

"The Association of American Physicians in grateful recognition of Sir. William Osler's distinguished services as one of its founders in October, 1885, and because of his beneficent influence on American Medicine, takes pleasure in extending to him sincere congratulations upon his seventieth anniversary, united with the fondest hope that his days of activity and happiness may still be many to complement a lifetime of service to humanity, so full of noble and fruitful achievements."

Dr. C. P. Howard presented a paper on "Functional Diagnosis of the Pluriglandular Syndrome in Acromegaly," which was discussed by Dr. H. S. Plummer.

Dr. H. S. Plummer presented a paper on "The Function of the Thyroid Gland."

Dr. E. C. Kendall presented a paper on "Chemical Identification of Thyroid Hormone."

Dr. Leo Loeb presented a paper on "Experimental Factors in the Compensatory Hypertrophy of the Thyroid Gland," which was discussed by Dr. H. S. Plummer and the discussion closed by Dr. Loeb.

Dr. T. B. Futcher presented a paper on "Cancer of the Pancreas," which was discussed by Drs. C. S. Bond and R. Fitz, and the discussion closed by Dr. Futcher.

Dr. L. B. Wilson presented a paper on "The Autopsy Service of the American Expeditionary Force."

Dr. M. H. Fussell presented a paper on "A New X-ray Sign of Perinephritic Abscess."

Dr. R. Fitz presented a paper on "Trench Nephritis at a British Hospital in France," which was discussed by Drs. T. McCrae and L. F. Barker and the discussion closed by Dr. Fitz.

Dr. A. D. Hirschfelder presented a paper on "An Experimental Study of Cloth Impregnation with Pediculicidal Substances," which was discussed by Dr. Plotz by invitation.

Dr. L. B. Wilson brought up the matter of a Bill introduced into the U. S. Senate regarding the use of animals in experimental work. It was moved, and seconded by Dr. Ford, That a Committee be appointed to take appropriate action concerning the Myers Bill, Senate File 1258, introduced into the United States Senate, June 2, 1919, and entitled "A Bill to Prohibit Experiments upon Living Dogs in the District of Columbia," etc. This was carried unanimously.

On motion of Dr. Dock, seconded by Dr. Futcher, a vote of thanks was given to Dr. McPhedran for the very interesting program and for the able way in which the meeting was conducted.

The following papers were read by title: "Chemistry of the Blood in Scurvy, Especially its Calcium Content," by Drs. J. A. Killian and A. F. Hess; "The Significance of Rickettsia in Relation to Disease," by Dr. R. P. Strong; "Report of a Case of Aneurysm of the Aorta Rupturing into the Left Innominate Vein," by Dr. J. B. Herrick; "Pneumonia Following Influenza," by Dr. E. L. Opie; "Generalized Syphilis in the Rabbit," by Drs. L. Pearce and W. H. Brown; "Principles in the Treatment of Certain Metabolic Disorders," by Dr. F. M. Allen; "The Pathology of Influenza," by Drs. G. Blumer and M. C. Winternitz.

Thomas McCrae, M.D.,
Secretary.

ADDRESS OF THE PRESIDENT

By ALEXANDER McPHEDRAN, M.D., LL.D.
TORONTO, CANADA

As our program is a very full one it is desirable that the President's address be brief. It is my first duty, as well as pleasure, to offer grateful thanks for the honor done me, even if the appointment comes in the course of seven years' service in the Council. The cordiality of my relations throughout these years has been such that I have never felt myself in fact what I am in theory, a stranger in a strange land. That this Association of American Physicians meets this peace year with a Canadian as President, I venture to look on as a happy omen for the success of that project so dear to all hearts that its exact form is the subject of disputation, the League of Nations. But the form in detail is of less importance to its vitality and usefulness than is the spirit animating its members. The generosity of you as Americans to us Canadians in according the privilege of membership in this Association, and election to its offices, is but one expression of the spirit which through so many years has led our peoples into even closer and more harmonious coöperation. The League of Nations can have no greater reason to believe in the possibility of its ideal than is provided by the cordial relations of our two countries, separated only by a long, imponderable line.

I feel that a reference to the war is more than justified by the services rendered to the allied cause by many of our members, and by the "supreme sacrifice" made by at least two of the most active and best beloved—Theodore Janeway and John McCrae. In the former we lost a very active and efficient associate, who contributed

much of the highest value to the scientific work of the Association. The latter, a brief time in our ranks, soldier and poet as well as physician, became widely known through his sonnet "In Flanders' Fields." Trumpet-voiced, the stirring lines gave utterance to the inarticulate thought of those who had died, and those who were dying and suffering to preserve our civilization, and found a universal response in the hearts of the civilian element of our nations in arms.

In the readjustment after the war we have to take account of the effect of military organization on medicine in all its aspects. First of all, many medical men, particularly the younger members of the profession who were attached as medical officers to combatant units and in the clearing hospitals, and those who worked on medical boards and did administrative work as well, have lost as much as four and a half years of that training and experience which well-directed postgraduate work and practice alone can give. These men deserve every consideration and help that can be extended to them in their desire for opportunities to refresh forgotten knowledge and in their efforts to reëstablish themselves in medical work of such nature as they choose.

The absorption of a large proportion of the male population into the army has spread through this continent new conceptions of the possibilities in the organization of communal life. Of these none is more striking than what the soldier has learned of the place of preventive medicine and of the importance of early treatment of any complaint. The man who was treated free while his pay went on in a well-organized and comfortable hospital, will have new standards of proper care of the sick, will demand more preventive medicine and will give eager support to any comprehensive scheme of health insurance. The whole public conception of the place of the physician has been radically altered. The physician, too, has gleaned many an idea of the importance of repeated examination and of close oversight in early diagnosis, particularly in disease in the chest, especially that "Achilles heel" of the man in the prime of life—tuberculosis, which takes a heavy and largely preventable toll of our adult population in the best period of their lives, as does also cardiac disease. Early diagnosis has long been an ideal: by the very great advance in medicine during the last five years

now the patient and physician alike have been presented opportunities for attaining it. They will not entirely forget: it is for the members of such organizations as this to reinforce their aims and desires.

Another group of diseases brought prominently to the notice of physicians is that much neglected field of functional disorders of which shell-shock is but a type. For years medicine has developed along the lines of laboratory work, of improved and rigidly systematized hospital organization of highly specialized departments and subdivisions. The revelations of the war necessitate a change in our attitude. We must take fuller account of the individual, we must consider the psychical side, the personal relation of man to man more closely if we would fulfill our whole duty as physicians. The development of medicine in the next decade will be greatly, if not predominantly, in its relation to psychology, normal and abnormal. The field is tremendous, vague and difficult. It has been neglected in medical schools: and so indefinite are the factors with which it deals, so little known in comparison with the elements of organic disease, that we lack clear-cut conceptions and well-defined terminology in dealing with the great group of the psychoneuroses. Yet in this field lies a very large proportion of all the cases, organic and functional, seen by both the general practitioner and by the consultant. The patient does not first consult the doctor because he has cardiac insufficiency or a cancer of the stomach or any specific disease, but on account of pain or discomfort. And pain or discomfort due to faulty psychology—to a fundamental error in the attitude to life in one or other of its phases—is as common as that arising from any demonstrable organic lesion. Physicians generally are too prone to concentrate attention on the probable organic disease and to treat the psychoneurosis or functional defect perfunctorily. Yet quite apart from the sheer pain and worry due to functional disorders is the obvious fact that they provide circumstances favoring the development of serious organic disease.

The last lesson I will allude to which we can learn from war conditions is the value of central advisory direction in promoting rapid progress in medicine. Individual workers or groups of workers were, in the war, coördinated by a commission of experts who

pointed out the problems to be solved. The urgency of the needs was splendidly met by the devotion and skill of the workers. If these gratifying results could be achieved during the stress and strain of the great conflict, much greater things are surely possible in the time of relief which follows. This Association should lead the way in thus pushing further the frontiers of knowledge.

Might it not be advisable to adopt a similar course in peace and appoint a standing committee to suggest problems in many fields, some of which are not receiving attention by members of this Association? The personnel of such a committee should represent all phases of work properly belonging to this Association, composed as it is of the leaders in all the methods of investigation pertaining to internal medicine. The recommendations of the Committee should stimulate much more systematic work in all fields than has hitherto been attempted. Many new clinical methods give results with no less definiteness than obtains in the laboratory. The requirements of modern medicine exact long, arduous, concentrated work for little increase in knowledge and demand much specialization. This results only too frequently in the lack of intimate correlation of the individual departments of medicine. But there are many intricate questions demanding for a complete answer the combined and interrelated efforts of the physiologist, the biochemist, the bacteriologist, the pathologist and the clinician. Where can we find the experts to undertake such important problems, with the hope of solution, if not in this Association, and who so able to coördinate the conclusions and make practical their application as the internist of large experience, who is familiar with laboratory work in all its phases? Such intensive coördinated work would result in broadening the bases of our knowledge, stimulate constructive thinking and kindle much enthusiasm, especially among the younger men. One such important problem would probably occupy a session, leaving the remainder of the meeting available for individual papers as at present.

This brings up the perennial question of the increase of membership. The proposals initiated by the late Theodore Janeway are on the order paper. The Council has given them careful consideration and their conclusions will be laid before the Association. May

I suggest that instead of a candidate on nomination being asked for a list of all his published papers, which in many cases takes up four or five pages, or even more, of the printed list which the Council can do little more than scan, he be required to submit the titles of not more than say five papers, and let them be those he considers his best, accompanied by reprints for the information of the Council. It is quality not quantity that affords the best basis on which to judge of his desirability for membership.

There is need for more nominations in order to afford the Council a longer list of applicants from which to select the most desirable candidates available for election to membership.

The *Transactions* for 1918 are very late in being distributed, through no fault of our energetic Recorder. Might it not be wise to instruct the Council to fix a date for their being issued, papers not ready to be included being inserted in an addendum to the following year's *Transactions?*

During the year five members have died—one Active, one Honorary and three Emeritus:

Joseph James Kinyoun, Major, M.C., U.S. Army, Washington, D. C., died at his home February 14, 1919, aged fifty-eight years. He was elected a member of this Association in 1901; had done distinguished service, devoting his time chiefly to sanitary work, and for eminent services rendered to the Venezuela Republic, being decorated with the Order of Bolivar in 1897.

James Tyson, Philadelphia, Pa., died at his home, February 21, 1919, aged seventy-seven years. He was one of the original members of the Association of American Physicians; was the first Secretary and took an active part in the organization of the Association. He was President in 1907–1908, and was elected an Honorary Member in 1915. He was the author of numerous text-books, the earliest being *Practical Examination of the Urine*, a book widely used in its day by a large number of medical schools, and later a text-book of *Practice of Medicine*. In his early years he devoted himself to pathology and later to the practice of medicine, of which he was professor in the University of Pennsylvania from 1899 to 1910, then becoming an emeritus professor. He had long been a visiting physician to the Philadelphia General Hospital and was interested

in many other institutions. He took a very active interest in this Association, attending its meetings with great regularity up to the very last, being present in 1916 and taking part in the proceedings. He had contributed many papers, the first being at the organization meeting of the Association in 1886 and the last one in 1911. In his death the Association loses a member who was greatly esteemed by all.

Frank Fairchild Wesbrook, Vancouver, B.C., died at his home, October 21, 1918, aged fifty years. He was elected an Active Member of the Association in 1898 and became an Emeritus Member in 1915. He had devoted himself to pathology and sanitary work chiefly. He was a member of many learned societies of the United States, Canada and Europe. He was appointed president of the University of British Columbia, Vancouver, in 1913.

James Jackson Putnam, Boston, Mass., died at his home, November 4, 1918, aged seventy-two years. He was an original member of the Association and retired to the Emeritus class in 1915. He devoted himself to neurology, being professor of that department in Harvard Medical School. He was very active and read many papers at the meetings of the Association, the last dealing with psycho-analysis, to which he gave much attention in his later years.

Frederick P. Henry, Philadelphia, Pa., died at his home, May 24, 1919, aged seventy-four years. He was an original member and was transferred to the Emeritus list in 1908. He was an active worker and read many papers, dealing chiefly with various blood conditions. He was professor of medicine in the Woman's Medical College of Pennsylvania since 1891.

APPLICATIONS OF THE PRAGMATIC METHOD TO PSYCHIATRY

By E. E. SOUTHARD, M.D.
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"*What difference would it practically make to anyone if this notion rather than that notion were true?* If no practical difference whatever can be traced, then the alternatives mean practically the same thing, and all dispute is idle." Such is one of the briefest formulations that Professor William James ever made of the pragmatic method. Again, there can be "no difference in abstract truth that doesn't express itself in a difference in concrete fact, and in conduct consequent upon the fact, imposed on somebody."

That the pragmatic method, altogether aside from any philosophic implications, must have very important relations to medicine would nowadays be denied by no man. In fact, the whole attitude of the medical man to medicine would not suffer if it should receive the designation "pragmatic." The very founder of the idea of pragmatism, Charles Peirce, used to speak of it as the "laboratory habit of mind." Pragmatism in medicine must have especially close relations with treatment and prognosis. This can be clearly seen from one of the better and longer statements of the nature of pragmatism as given by James in Baldwin's *Dictionary of Philosophy and Psychology:* Pragmatism is "the doctrine that the whole meaning of a conception expresses itself in practical consequences, consequences either in the shape of conduct to be recommended or in that of experiences to be expected, if the conception be true; which consequences would be different if it were untrue, and must be different from the consequences by which the meaning of other conceptions is in turn expressed. If a second conception should

not apear to have other consequences, then it must really be only the first conception under a different name. In methodology it is certain that to trace and compare their respective consequences is an admirable way of establishing the differing meanings of different conceptions."

It is my object in the present paper to apply pragmatic principles to some problems of psychiatry.

1. Psychiatry and Clinical Neurology. *In the first place, does psychiatry exist as distinct from neurology?* It can be pointed out that the research basis of psychiatry and of clinical neurology is a unit, namely, theoretical neuropathology, considered in both structural and functional aspects. Let us, however, apply the pragmatic method. Is psychiatry only clinical neurology under a different name? The moment we trace and compare the respective consequences of these two ideas, we perceive that clinical neurology leads to a quite different effect upon the patient from that to be expected when psychiatry approaches him. Psychiatrists and clinical neurologists have had no identical education as clinicians, and they have not the same outlook. This is a practical situation which has pragmatic consequences. It is simply a pious wish when we state that clinical neurologists and psychiatrists are all really nothing but neuropsychiatrists. Perhaps they ought to be and perhaps they soon will be, but they are not. It makes a great deal of difference to the patient whether he is approached by a psychiatrist or by a clinical neurologist.

I have elsewhere gone into more detail upon this matter, referring especially to the different points of view, *e. g.*, toward mild cases of schizophrenia (dementia precox) and cyclothymia (manic-depressive psychoses), maintained by neurologist and psychiatrist respectively. I will not here discuss the point further.

Clinical neurology and psychiatry are pragmatic entities, for they have different consequences when their points of view are applied to the victims of disease

2. The So-called "Unity of Insanity." Turning to the subject matter of psychiatry, the largest question hangs upon whether we define mental diseases as a unit or as a set of entities. English writers, among them some of the more subtle, such as Charles Mercier, have for years plumped for the unitarian view. One must

have a certain respect for any Anglo-Saxon view of the topic, seeing that it no doubt has a certain relevance and practical applicability. However, I think the progress of psychiatry proves, not only that mental diseases can be analytically split up into logical entities, but that these logical units have pragmatic value. At the same time that a thinker like Mercier insists upon the "unity of insanity," he also insists upon grades of responsibility in medicolegal cases and claims to be one of the earliest to have made this distinction. In fine, Mercier lugs in at the finish what we practically want in the matter of subdivisions within psychiatry. If we look more narrowly at other British authors, we find that they often dispose of the unity question in mental diseases by throwing into the field of "nervous" diseases everything which does not handily fit a preconceived legal definition of insanity. This again may comport with Anglo-Saxon notions of practicality and may have a certain relevance from the standpoint of law courts. But assuredly we do not get on very measurably in psychiatric research, if we simply redistribute our material to suit some non-medical criterion, such as some standard of the practical responsibility of mental cases.

It seems to me that the progress of psychopathic hospitals, in the few places in the world where they have been rigorously tried out, shows beyond cavil that psychiatry is an art dealing with numerous entities. Possibly (according to a rough enumeration from popular systematic works) there may be between eighty and one hundred of these practical entities.

The pragmatic question is, what difference does it make to the patient whether he is said to be affiliated with one or the other of these entities? I am not sure that I can prove that there is a different "conduct to be recommended" or different "experiences to be expected" (to use James' phrases) for all of these eighty-odd entities. But I am entirely sure that it makes a great difference to the patient whether he is to be placed in one of ten or a dozen major groups of these entities. Perhaps I entirely miss the point of the British contentions for the unity of insanity; but I really cannot see that their viewpoint has a leg to stand upon when we contemplate the present nosological situation. It certainly makes a great deal of difference to the patient, as well as to the social unit in which he lives, whether we regard the patient as a victim of neurosyphilis or

whether we regard him as a victim of alcoholic psychosis. Now, possibly the English authors would wish to exclude the victim of neurosyphilis and of alcoholic mental disease from the realm of insanity altogether. Very well—let this happen. We should then at best attain a conception of the unity of insanity only by greatly diminishing its contents, as ordinarily conceived. But would any author deny that it makes a great deal of difference to the patient whether he is a victim of psychoneurosis or of some depression falling in the group termed by Kraepelin manic-depressive psychosis (which I think might as a group better be termed the cyclothymic group)? Now again, if the unitarian wishes to diminish the field of insanity by cutting off the psychoneuroses, so be it. Again we shall attain unity by a Procrustean process. The psychiatrist will give up any insight he may have into the psychoneurotic and hand his patient forthwith over to the clinical neurologist. Yet the research basis for the understanding of psychoneuroses is no doubt identical for both the psychiatrist and the clinical neurologist. Again the pragmatic method should be applied. If it is true that it is going to make a great difference to the patient whether he is regarded psychiatrically or neurologically, then we must decide that there are real differences under discussion.

Parceling out the psychoneuroses and the cyclothymias to the neurologists and the psychiatrists, respectively, may seem logically the right thing to do. Pragmatically I believe it will have, not only practical, but evil consequences if we execute this partition.

3. Diagnosis by Orderly Exclusion. Dismissing the question of the unity of insanity, I wish to approach a few other pragmatic questions in psychiatry and to hang them upon the order concept. Last year I advocated before the Association in a paper "*Diagnosis per Exclusionem in Ordine:* General and Psychiatric Remarks" the application of the principle of order in psychiatric diagnosis, and called attention to the existence of eleven major groups of entities which seemed to me to have practical value. Of course I was aware that the principle could be applied to many other branches of medicine, and I am glad to say that in correspondence with Dr. Richard C. Cabot, we have together concluded that the principle might very effectively be installed at an early date in many of the specialties, if not in the whole of medicine. As Dr.

Cabot has said to me, if one gets hold of a *list* of things it is manifest that said list may be turned into a *sequence* or order and that this sequence or order may have practical value. I shall not here repeat the considerations of the above-mentioned paper, at least to any extent; but I wish to claim that the application of the order concept is an example of pragmatic method. It makes a difference to the patient both in "conduct to be recommended" and "experience to be expected" whether we approach him diagnostically in an orderly fashion.

4. Neurosyphilis and General Paresis. It has in the past made a good deal of practical difference to many psychopathic patients that they have not been primarily considered as possibly victims of neurosyphilis. Time was when the Wassermann serum reaction was taken only in cases in which one suspected general paresis. Nowadays so protean have been proved to be the forms of neurosyphilis that for practical purposes no mental patient can fail to be thought possibly syphilitic. That hypothesis must be disposed of one way or the other.

But if neurosyphilitic, what form of neurosyphilis is in play? It makes a great deal of difference to the patient whether we set up the hypothesis that he has general paresis (with all the evil prognostic connotations of that entity) or whether we limit our initial idea to his being merely neurosyphilitic. An application of the pragmatic method to the orderly diagnosis of the subentities of the neurosyphilitic group would make us consider at some point the *non-paretic* forms of neurosyphilis. We should, in the pragmatic interest of the patient, keep our diagnostic ideas in solution at the level of undifferentiated neurosyphilis rather than leap to the diagnosis "general paresis." We have practically seen a great deal of evil happen to patients by reason of these premature leaps to the diagnosis "general paresis," on the basis of a few clinical similarities to the entity as described in books. There is, therefore, much scope for the application of pragmatic method in the field of neurosyphilis.

5. Diagnostic Precession of "Focal" versus "Symptomatic" Cases. To facilitate the rest of my discussion I will here reproduce the eleven groups of mental disease from my paper on "*Diagnosis per Exclusionem in Ordine.*"

MENTAL DISEASE GROUPS (ORDERS)

I.	Syphilitic	Syphilopsychoses
II.	Feeble-minded	Hypophrenoses
III.	Epileptic	Epileptoses
IV.	Alcoholic, drug, poison	Pharmacopsychoses
V.	Focal brain ("organic," arteriosclerotic)	Encephalopsychoses
VI.	Bodily disease ("symptomatic")	Somatopsychoses
VII.	Senescent, senile	Geriopsychoses
VIII.	Dementia precox, paraphrenic	Schizophrenoses.
IX.	Manic-depressive, cyclothymic	Cyclothymoses
X.	Hysteric, psychasthenic, neurasthenic	Psychoneuroses
XI.	Psychopathic, paranoiac, et al	Psychopathoses

Why is Group V of the Encephalopsychoses placed prior to Group VI, the Somatopsychoses? Logically, it might well seem that we should approach, in the process of diagnosis, the somatic diseases that give rise to mental symptoms prior to the focal brain diseases that produce mental symptoms. But logic is not practice. In the general hospital clinics, where somatic diseases, non-nervous in nature, are habitually approached logically prior to the nervous and mental diseases, we have not found much progress in psychiatry or much grasp of the psychiatric point of view. Mental cases will for many years to come in our hospital practice, devolve more seriously upon the attention of neurologists and psychiatrists than they will upon the attention of internists. If a man has mental disease and if one has excluded the great groups of syphilis, feeble-mindedness, epilepsy, and alcoholism (with all their practical social implications), then one naturally desires to clear up other large brain aspects of this mental case. Although we are in possession of numerous data to show that mental symptoms may be merely symptomatic of bodily (non-neural) diseases, yet there is no doubt that the nervous system exerts in some ways a prior claim on the attention. Perhaps the practical answer would be that in internists' clinics, the order of logical consideration should be reversed and Group VI placed before Group V, whereas in psychiatric clinics the order might remain as stated. Let me insist at this point on something which is logically clear, but practically not always envisaged. *This system of orderly exclusion in diagnosis has nothing whatever to do with the practical order in which data are collected.* It is a plan to be put into effect *after the data are all in hand.* It does not matter whether the data about the pupils or the reflexes are

chronologically collected before the data concerning bodily infection. The question is one of logical, not of chronological, priority. In the end, however, I am willing to acknowledge that the question, whether the encephalic or the non-neural somatic conditions should be diagnostically placed in the order I recommend, is an open question. The question can be answered in the long run only pragmatically.

6. Diagnostic Precession of Schizophrenic versus Cyclothymic Cases. One other example may be offered looking in the same direction. I have placed the schizophrenoses (dementia precox, etc.), in Group VIII, ahead of the cyclothymoses (manic-depressive, etc.), Group IX. Now it might be pointed out that as manic depressive phenomena are more nearly normal than schizophrenic phenomena, it should be well to consider the patient normal before we consider him abnormal. Let the patient be regarded as innocent of mental symptoms before he is regarded as guilty of such. Well, the pragmatic answer to this question is that it appears to have important practical consequences whether we consider a patient schizophrenic logically prior to our considering him cyclothymic. A group of schizophrenic symptoms is much more convincing as to a patient's being a victim of the disease schizophrenia than is a group of cyclothymic symptoms convincing as to his being a victim of cyclothymic disease. Just in virtue of the quasi-normality of the ups and downs in mood of the manic-depressive does it transpire that practically every form of mental disease is capable of showing these ups and downs in mood. By consequence if we fix our minds upon cyclothymic phenomena, we are rather inclined to premature fixation of our minds upon the diagnosis of the entity manic-depressive psychosis. Seeing cyclothymoid symptoms, we rush to the idea of the cyclothymic entity. In short a group of schizophrenic symptoms is much more "pathognomonic" than a group of cyclothymic symptoms. It was upon this pragmatic basis that Group VIII was placed before Group IX.

Why should we place the psychoneuroses in a Group X, following the schizophrenias and cyclothymias? I am bound to admit that this placement was an exceedingly practical one. We have in psychopathic hospital practice seen so many cases in which the diag-

nosis "nervous prostration" has been affixed to a patient who was really a mild example of schizophrenia or of cyclothymia (and this much to the therapeutic detriment of the cases in question) that it seemed wise to relegate the psychoneuroses to a subsequent position in the diagnostic list for orderly exclusion.

7. Placement of Involution-melancholia. Another example of the application of the pragmatic method is in the question of involution-melancholia. Controversy rages as to whether the involution-melancholias belong in the senile group (in my own arrangement, Group VII, the Geriopsychoses) or whether they belong in the cyclothymic (manic-depressive group) Group IX of the above list. Logically there might be some argument for placing the involution-melancholias among the senile and presenile conditions. The very *term* involution suggests this. However, it seems to me that we must grant that we know next to nothing (and pragmatically I should say absolutely nothing) about the etiology and genesis of involution-melancholia. No doubt there is a darkling idea that involution-melancholia is somehow an endocrine affair. We know nothing about the etiology and genesis of manic-depressive psychoses. But here the pragmatic method allows us to employ even our ignorance to advantage. There is not the slightest doubt that to place a case in the senile or presenile sub-groups of the Geriopsychoses is to give the case an evil prognosis with respect to tissue destruction and degeneration, perhaps unjustly and harmfully.

To place the involution-melancholias in the senile-senescent group is to cause certain experiences to be expected. Now, practically, we know that such experiences are not always to be expected in involution-melancholia, in short that clinical deterioration is not always found to suggest brain tissue degeneration. Pragmatically speaking, therefore, it seems to me that the reply as to the placement of the involution-melancholias is unconditionally to place them in the cyclothymic group, as compared with the senile-senescent group—and this despite our dense ignorance of the nature of involution-melancholia.

Summary. 1. Psychiatry should more and more adopt the "Laboratory habit of mind," become more and more pragmatic, and bring itself in line with the rest of medicine.

2. Seven applications of the pragmatic method to psychiatry are offered:

(*a*) It makes a difference to the patient whether he is seen by a psychiatrist or by a clinical neurologist: There is thus for the moment a real difference between psychiatry and clinical neurology, though the future may destroy that difference and produce "neuro-psychiatry."

(*b*) It makes a difference to the patient whether we take "insanity" as a unit or as a collection of entities: The pragmatic rule decides in favor of a pluralistic view of mental diseases.

(*c*) The principle of *orderly* exclusion in the diagnosis of complicated cases is of pragmatic value.

(*d*) Especially is this true of the diagnostic field of neurosyphilis, where it is important to maintain the *non*-paretic hypothesis as long as possible in the interest of the patient's therapy.

(*e*) Opinions might differ as to the advisability of entertaining the hypothesis of focal brain disease before or after the hypothesis of somatic (non-neural) disease in a given case: The pragmatic rule might decide one way for general hospital clinics and the other way for mental clinics.

(*f*) Schizophrenia should be eliminated before cyclothymia on the pragmatic basis, for a group of schizophrenic symptoms is much more decisive for dementia precox than a group of cyclothymic symptoms is decisive for manic-depressive psychosis.

(*g*) The pragmatic method decides that in the face of complete ignorance of its true nature, involution-melancholia is better placed in the cyclothymic (manic-depressive) group than in the senile-senescent group, if it is to be placed in either group.

DISCUSSION

Dr. A. Meyer said: Pragmatic and practical experience leads us to speak of facts we meet in our cases, which are best looked upon as *factors* to be studied for their *effects* and their *origins* and our *means of modifying them*. The principal objection to Southard's formulation is that it still stands on the ground of a nosology which means to label each person with one nosological term, where any physician would rather enumerate the facts at hand, the parts, organs and functions involved, the possible common links in the disorder, and the problems to be attacked—rarely but one, and oftener several in free combination.

A CASE OF PERFORATED GASTRIC ULCER, WITH ABSCESS FORMATION; PERFORATION THROUGH THE LUNG, WITH SPONTANEOUS RECOVERY

By JULIUS FRIEDENWALD, M.D.
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Cases of perforation of the stomach and duodenum leading to subphrenic abscess, with rupture through the lung, are of sufficient rarity to be of interest. The patient, Mr. W. P. G. aged fifty-one years, was first seen in consultation with Dr. O. N. Duvall on April 5, 1917. His family and personal histories were entirely negative and unimportant, except as related to his gastro-intestinal tract.

The patient had complained of gastric disturbance for the past twenty-five to thirty years. During this period there was frequent indigestion, consisting mainly of fulness after meals and belching. For the past eight to ten years the attacks of indigestion were periodic, lasting for three or four weeks to several months at a time. These attacks were characterized by pain in the stomach appearing two hours after meals, more marked after solid food, which were relieved by the use of soda or by rest in the recumbent posture. There were eructations of acid matter, and pyrosis was frequent. Hunger pains were often present, which were relieved by food, the pain recurring two or three hours later. There were periods of six months or more, during which the patient enjoyed perfect health, free from all digestive symptoms. He was always constipated; was frequently nauseated; vomited at times; however, he had at no time vomited blood or food eaten the day previously, nor had he passed tar-colored stools. The appetite was good; there was no history of jaundice. The patient complained of hemorrhoids. He

had had lumbago and was affected with nocturia, micturating once during the night; there was no history of swelling of the feet or eyelids; no dizziness. The patient denied having had lues or gonorrhea.

Present Illness. After some weeks of indigestion, of such a character as has already been described, the patient was suddenly seized with severe agonizing pains over the left upper abdomen, which required the administration of two hypodermic injections of morphin for relief. At that time the abdomen was distended and there was present a distinctly tender epigastric area. The following day he developed dull pain in the left kidney region, which radiated toward the epigastrium. This pain persisted for ten days and was accompanied by a temperature ranging between 101° to 103°. He developed a cough and hiccoughing, which were shortly followed by a purulent expectoration; he expectorated during the first day about one quart of pus. When the expectoration began the temperature receded and the pain became greatly diminished. At this stage the patient was admitted into the Union Protestant Infirmary (April 6, 1917).

Examination. The patient is a thin, poorly nourished individual, with much respiratory discomfort and a facial expression of distress. The skin and mucous membranes were pale; the ears and eyes were normal. The alæ nasi moved rapidly in respiration. The tongue was coated; there was a marked pyorrhea alveolaris.

Chest. The physical findings of the chest were negative, except that there was some impairment of the percussion note on the right side over the region of the scapula. However, on auscultation nothing abnormal could be discovered in this region. The heart was not enlarged; the sounds were clear; there were no murmurs.

Abdomen. The abdomen was somewhat distended. The recti muscles were spastic. There was a distinctly tender area in the epigastrium as well as tenderness in the left lumbar region, over which there was a burn caused by hot applications to that region. The liver extended one finger's breadth below the costal margin. No masses were felt anywhere. The genitals were normal; there were no glandular enlargements. The reflexes were present and were equal and active on both sides.

Blood examination: Total leukocyte count, 11,900. Differential count: Polynuclears, 70 per cent.; small mononuclears, 25 per cent.; large mononuclears, 4 per cent.

Urinary Examination. The urine had a specific gravity of 1022; presented a trace of albumin, but was otherwise negative.

Roentgen-ray Examination. Stomach: High stomach, rapid expulsion, defect at pyloroduodenal junction, revealing an ulcer at this area.

Chest: No emphysema or thickened pleura. Dilatation of bronchi at bases showed bronchiectasis. Cloudy infiltration below the right clavicle.

NOTE.—Since admission into the hospital the patient expectorated about one pint of pus the first day, the quantity decreasing each day since that time; finally, on April 11, he expectorated but 50 c.c. of pus, and on April 12 there was no further expectoration. The pus was thick and creamy and of a putrid odor, containing colon bacilli as well as streptococci in abundance.

On admission the patient's temperature was 100°, which gradually fell, so that after April 12 it remained normal. His appetite improved and he began to feel much stronger. He left the hospital on April 12 greatly improved in health, and has remained well since.

It is clear that the patient must have had a gastric ulcer, persisting over a long period of time. This became evident from the long ulcer history, with periods of remission, as well as from the definite roentgen-ray signs of ulcer, which were revealed at the time of his entrance into the hospital. The sudden onset of abdominal pain, requiring two hypodermic injections of morphin for relief, indicated the onset of the perforation, which was followed by fever, the formation of subphrenic abscess and finally a perforation through the lung, with the expectoration of pus. After the abscess was thoroughly evacuated the patient made a spontaneous recovery.

In an extensive monograph published in 1894 Maydl reports 179 cases of subphrenic abscesses, the stomach and duodenum being the source of infection in 35.

Subphrenic abscess may be either intraperitoneal or extraperitoneal, the latter being more frequent on the left side. Since the

falciform ligament acts as a firm wall the abscesses are found usually on one side only. The right-sided ones are between the diaphragm and the liver. The left-sided ones have the diaphragm above and below, and for boundaries some part of the stomach, spleen, transverse colon and left lobe of the liver. The origin of the infection may arise from any one of these organs. The abscess appears as an encysted localized peritonitis and the cavity may be very small or large enough to hold several liters of pus or pus with gas. The pus may be thick or thin, putrid or free from odor, or colored with blood. The gas may arise from the opening to the organs, which may contain gas or may be due to the gas bacillus of Welch.

In Maydl's series of 179 cases, of which 47 contained gas, 20 were due to perforation from the gastro-intestinal tract, 18 to secondary perforation (16 into the lung and 2 into the gastro-intestinal tract) and 9 to the gas bacillus, no perforation having been observed. The organisms most frequently observed in the pus are the tubercle bacillus, staphylococcus and the colon bacillus.

Osler notes that the presence of the colon bacillus in the pus indicates the gastro-intestinal tract as the origin of the infection. If the abscess is not disturbed it is liable to perforate the diaphragm infecting the pleural cavity and lung, and complete evacuation may take place through the lung; thus spontaneous cure might be effected, as was observed in our case.

In perforation of gastric ulcers producing subphrenic abscesses the symptoms may develop slowly, but, as a rule, the pus accumulates rapidly and the symptoms are usually exceedingly acute. There is often a sudden severe pain in the epigastrium or hypochondrium radiating to the shoulders, with marked dyspnea due to pressure on the diaphragm. There is usually present, in addition, vomiting, hiccough and marked weakness and acceleration of the pulse. Fever with chills and sweats are not uncommonly observed. Perforation of the diaphragm and rupture into and through the lung next occurs, with complete evacuation through a bronchus.

There are but four cases recorded similar to ours in which perforation from a gastric ulcer was followed by rupture through the lung.

Case I.—Leyden.[1] The patient, aged seventy years, was suddenly taken with acute abdominal pain. There appeared to be some obstructive condition of the bowels, as it seemed impossible to produce a bowel evacuation; finally, after three days, the bowels moved, but fever then appeared, with chills and dulness on the right side of the chest up to the middle of the scapula. There was then a sudden expectoration of a large quantity of bloody fetid pus.

Case II.—Juliusberge.[2] A. B., aged forty-three years, was treated for rectal hemorrhages which had weakened the patient very materially. He also complained of digestive discomfort, loss of appetite; pressure and fulness in the region of the stomach, especially after meals; belching; pain and flatulency. The patient was suddenly taken with hematemesis and pain in the stomach and fainting. On examination the epigastrium was found markedly distended and a mass was formed in this region; chills and fever appeared; finally the patient expectorated a large quantity of pus.

Case III.—Neusser.[3] A female patient, aged thirty-seven years, observed a swelling in the abdomen above the umbilicus. In addition there were numerous digestive symptoms, loss of appetite, green stools and pain after food. A cough appeared and was finally followed by the expectoration of pus. The patient died and at autopsy a perforated gastric ulcer was found, leading to a pus cavity in the lungs.

Case IV.—Nowack.[4] A maid, aged nineteen years, had frequently been affected with gastric disorder. She was suddenly seized with sharp pain in the lower abdomen. The pain increased and the abdomen became swollen. The patient began to vomit and became very weak. The pain in the region of the liver increased; the pulse became rapid and weak and the temperature subnormal. A perforation of the stomach was diagnosed and an operation performed. From one to two liters of fibrinous fluid were found in the abdominal cavity. The patient died and at autopsy an abscess of the lung was revealed, produced by the perforated gastric ulcer.

[1] Ztschr. f. klin. Med., i, 320.
[2] Berl. klin. Wchnschr., 1874, p. 643.
[3] Wien. med. Wchnschr., 1884.
[4] Schmidt's Jahrb., 1891, Nos. 9 and 10.

EPIDEMIC NON-SUPPURATIVE ENCEPHALITIS, ENCEPHALOMYELITIS AND MENINGO-ENCEPHALO-MYELO-NEURITIS[1]

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(ABSTRACT)

Introduction

During 1918–19 there has been prevalent in the United States an epidemic disease, now known to be an inflammation of the nervous system, involving predominantly the brain (encephalitis), and sometimes the spinal cord (myelitis), but often involving both brain and cord (encephalomyelitis) or even including also to a certain extent the meninges and the peripheral nerves (meningo-encephalo-myelo-neuritis). Observations of the disease in this country have been reported by K. A. Menninger, Peter Bassoe, Josephine B. Neal, O. L. Pothier, Beverley R. Tucker, Henry M. Thomas and E. W. Schnoor.

The epidemic in the United States must, I think, be looked upon as a part of a pandemic occurrence of the same disease, for epidemics closely resembling the outbreak here have been, since 1917, reported in many different parts of the world. The first outbreak in this pandemic to be observed seems to have been an epidemic of the disease occurring in Vienna in the winter of 1916–17 and reported by von Economo who called the malady, unfortunately perhaps, "encephalitis lethargica." Another outbreak occurred in Australia,

[1] This paper was published in full in the American Journal of the Medical Sciences for February and March, 1920.

especially in Queensland and in New South Wales, in 1917, the mysterious disease being reported in a paper by Breinl. In the spring of 1918, an epidemic of the disease was recognized to exist in France, where Netter described it as encéphalite léthargique épidémique.

In March and April of the same year (1918), the malady appeared in epidemic form in fifty-one sanitary districts in England, and especially in London, Birmingham, Sheffield and Leicester, and was reported by Harris, Hall, Batten and Still, Crookshank, Melland, Christopherson and Mawer, S. A. K. Wilson, E. F. Buzzard, S. K. Vaidya and others. In the latter part of 1917 and in 1918, cases were met with in Uruguay; they have been recorded by L. Morquio of Montevideo. Evidently, therefore the outbreaks recorded in Europe, in North America, in South America, and in Australia, indicate a world-wide distribution of encephalitis in epidemic form.

Personal Observations

My own experience in the present epidemic dates from February, 1919, since when up to June, 1919, I have had some ten cases in which the diagnosis of acute or subacute encephalitis or encephalomyelitis has been made; through the courtesy of Dr. H. M. Thomas, of Dr. John Howland and of Dr. Sydney R. Miller, who have had a number of these patients under their care, I have been permitted to see several additional cases. I hope to report my own material more fully later on, but desire, on account of the great interest attaching to the subject, to present at this meeting summaries of the findings in several of the cases observed.

Case I.—*Mesencephalopontilobulbar type with infectious ophthalmoplegia, facial paralysis, dysmasesia and dysphagia.*

Man, aged twenty-seven years, from Marion, S. C., referred by Dr. E. R. Dibble; studied in association with Dr. Ernest Cross, Dr. S. R. Miller and Dr. H. M. Thomas, February 20, 1919.

Complaints. Drooping eyelids; inability to move upper lip; accumulation of food between teeth and cheek; difficulty in swallowing liquids.

Onset. Three weeks before (nine weeks after an attack of influenza) he began to see double; this diplopia was absent in the morning after sleep at first, but soon it became constant. About the same time he exhibited

a paralysis of the right face, with double ptosis and strabismus. Slowly the lips, and the left face, became paralyzed.

Positive Findings on Examination. Bilateral ptosis; paresis of right lateral rectus; anisocoria, the right pupil being larger than the left and more sluggish; bilateral facial paralysis; partial paralysis of right masticatory muscles. Tachycardia; pulse, 108; gastric hyperacidity (total acidity, 71 per cent.); emaciation (twenty-five pounds under ideal weight.)

Blood.

W. B. C., 6200; P. M. N., 62 per cent.; SM., 23.2 per cent.; WaR = 0.

Cerebrospinal Fluid. Cell count, 30; all small mononuclears; globulin ++++; WaR = 0.

Course. Gradual improvement.

Summary. Ophthalmoplegia externa et interna (N. III and N. VI.); bilateral facial paralysis (N. VII); right dysmasesia (motor N. V.); dysphagia (N. IX); tachycardia (N. X.).

Principal Localization. Mesencephalon; pons; medulla oblongata.

Diagnosis. Encephalitis acuta.

Result. Patient is slowly recovering.

Case II. *Meningotelencephalic type; with symptoms of meningeal irritation and delirium.*

Man, aged forty-eight years, from Fort Mitchell, Ala.; referred by Dr. W. W. Stewart, of Columbus, Ga., and by Dr. Allen, of Oswitchee, Ala.; admitted to private ward, Johns Hopkins Hospital, March 3, 1919. Studied in association with Dr. S. V. Irwin and Dr. H. A. Ward, of the Resident Staff, and with Dr. H. M. Thomas and Dr. C. M. Campbell as consultants.

Complaints. Patient confused, complaining of pain in back of head for five weeks. History obtained from sister and from letters of physicians.

Onset. About January 21, 1919, sudden onset, with intense headache (frontal and occipital) and backache. Temperature, 104° on the first day, but in four or five days it fell to 99.5°; pulse 90; blood-pressure, 140; extremely nervous; mind wandering; incoherence; dry skin; oliguria and albuminuria. Uremia suspected; was bled twelve ounces; hot packs; purgation; milk diet; improvement; condition about same until February 20; then exacerbation; mental disturbance; tendency to violence, suicidal threats. Drowsy, toxic. (History of alcoholism and of sulky spells and of irritability, with progressively increasing feebleness, rapid loss of weight and some mental disturbance at times for six to eight months.)

Positive Findings on Examination. Drowsy; sluggish pupils; right deafness; slight dry bronchitis; rigidity of neck and back; passive movement of neck painful; tender right abdomen; Kernig, +; Brudzinski, +; pyorrhea alveolaris; emaciation (thirty-five pounds).

Laboratory Tests. Blood. W. B. C., 22,850; P. M. N., 90 per cent.; WaR = 0.

Cerebrospinal Fluid. 1. March 3 = clear; increased pressure; WaR., negative in quadruple quantity; globulin, ++++; cells, 97 (nearly all s.m.); gold-sol curve = combined paretic and meningitic type.

2. March 7 = clear; increased pressure; WaR. = 0; globulin, ++++; cells, 133; gold-sol curve = same as March 3.

3. April 25 = clear; increased pressure; WaR. = 0; globulin, ++++; small mononuclear cells, 33. No bacteria in smears or in cultures.

Urine. Albuminuria; casts present; R. B. C. + and W. B. C. +; phthalein output, 70 per cent. in two hours.

Course. Much relieved by lumbar punctures; gradual improvement; gained twenty-two pounds before discharge from the hospital on April 30 (seven weeks after admission). Letters since report excellent health.

Summary. Fever; delirium; incoherence; drowsiness; uremia suspected; later, symptoms of meningeal irritation; sluggish pupils; leukocytosis; spinal pleocytosis; nephropathy; undernutrition.

Localization. Telencephalon; mesencephalon; meninges.

Diagnosis. Meningo-encephalitis acuta in a man suffering from chronic alcoholism, chronic nephropathy and marked undernutrition.

Result. Recovery.

Case III.—*Acute encephalitis causing hemiparesthesia, with glycosuria and muscular asthenopia.*

Man, aged forty-seven years, from Marietta, Ohio. Came for diagnostic study March 13, 1919.

Complaints. Numbness of left arm, loin and leg, with tingling (but without loss of strength or motility) and transient glycosuria following "influenza," about two months earlier.

Onset. On January 17, 1919 suffered an attack of "influenza"; two days later numbness and tingling appeared; this was followed, ten days later, by glycosuria, which, on a diet, ceased in seven days, though the numbness and tingling grew progressively worse. History of lues eighteen years ago. Diabetes in the family.

Positive Findings on Examination. Obesity (thirty pounds); muscular asthenopia; slight tachycardia (104); oral sepsis (five teeth to extract for periapical granulomata; pyorrhea); slight albuminuria and cylindruria; blood-pressure, 163/94; moderate dilatation of aorta; ileal stasis; chronic prostatitis.

Laboratory Tests. Blood. W. B. C., 10,000; P. M. N., 76 per cent.; S. M., 17.2; WaR = 0; blood sugar, 210 mg.

Stomach Contents. Free HCl, 36; T. A., 89.

Cerebrospinal Fluid. Clear; pressure not increased; globulin, +; cells, 30, all small mononuclear; WaR = 0.

Course. Soon improved in general health, but numbness persisted.

Summary. "Influenza," followed by hemiparesthesia sinistra, glycosuria and muscular asthenopia, in a man of diabetic family, with oral sepsis, arterial hypertension, obesity and with a luetic history.

Localization. Diencephalon (thalamus or regio subthalamica?); mesencephalon. Meninges (a sensory tract case).

Diagnosis. Meningo-encephalitis acuta; obesity; oral sepsis; atherosclerosis.

Result. Recovery, with slight sensory defect.

CASE IV.—*Parkinsonian type.*

Woman, aged forty-six years, from Fairmont, W. Va., referred by Dr. George H. Brownfield. Studied March 17, 1919.

Complaints. Double vision; weakness; nervousness; depression; insomnia.

Onset. Eight weeks ago influenza; six weeks ago began to have "difficulty in seeing" and diplopia. The eyelids drooped; weakness felt, requiring bed; nervousness; dizziness; constipation; her physician said her "mind wandered."

Positive Findings on Examination. Temperature, 99° to 100°; pulse, 112; facial mask; bilateral ptosis; left facial paresis; twitching of upper lip and of tongue; poor convergence of eyes; slight nystagmoid movements; tender masseters (sign first observed and emphasized by Professor H. M. Thomas); asthenia; emaciation (twenty pounds); slight struma; slight gingivitis; impairment of mastication.

Laboratory Tests. Blood. W. B. C., 10,000; P. M. N., 82.8 per cent.; S. M., 12.8 per cent.; WaR. = 0.

Stomach Contents. Free HCl = 0; T. A., 30; ac., per cent.

Urine. Trace of albumin and few casts.

Cerebrospinal Fluid. March 18, clear; pressure not increased; globulin, +; two small mononuclear cells; no fibrin; WaR = 0.

April 4, clear; pressure not increased; globulin, +; seven cells; WaR = 0.

Course. Under observation and treatment in the Johns Hopkins Hospital, March 18 to April 14; temperature, 99° to 100°; pulse, 90 to 110; gained six pounds; twitching ceased; expression of face returning; also strength.

Report on June 1, 1919. Gained fifteen pounds after leaving hospital. Feels well, except that vision (accommodation?) is still imperfect.

Summary. Ophthalmoplegia; left facial paresis; facial mask; twitching of lips and tongue; nystagmoid movements; tender masseters; asthenia.

Principal Localization. Telencephalon; diencephalon; mesencephalon; pons; medulla oblongata.

Diagnosis. Encephalitis acuta; achylia gastrica; myomata uteri; undernutrition.

Result. Recovery.

CASE V.—*Lethargic type with ophthalmoplegia, facial paresis and mask.*

Woman, aged thirty-three years, colored, married, entered Ward O, Johns Hopkins Hospital, March 22, 1919.

Complaint. "Misery in eyes and head."

Onset. One week before admission, attacked suddenly while at work with vertigo and diplopia. The former passed off; the latter persisted. Since onset, severe headaches, keeping patient in bed. Feeling of "sand in the eyes;" anorexia; asthenia; marked drowsiness, even when talking; dysphagia; food accumulates in the right cheek.

Positive Findings on Examination. (Dr. Arthur Bloomfield, Dr. Hermann and others.) Temperature, 99°; pulse, 100. Accommodation-paresis; unable to read for one week; diplopia; lacrimation; slight nystagmus; all external muscles of eyes weak, though no complete paralysis; all movements of eyes sluggish and uncertain; weakness and tenderness of masseters on ninth day (Thomas's sign); bilateral facial paresis (left and right); mask-like face; sweating of face (right and left); slight tachycardia.

Laboratory Tests. Blood. W. B. C., 9120; P. M. N., 75.5; S. M., 16; WaR = 0. Blood culture = 0.

Urine. = 0.

Cerebrospinal Fluid. Drawn twice; both specimens contained blood. WaR = 0 in blood-stained fluid.

Course. More or less lethargic during stay; mask-like expression; facial sweating; paresis of muscles innervated by NN. III, IV, V, VI and VII continued while under observation in the hospital.

Summary. A sudden attack of vertigo and diplopia, with slight fever, headache, anorexia and asthenia, followed by general paresis of internal and external muscles of eyes ("infectious ophthalmoplegia"), paresis and tenderness of masticatory muscles, bilateral facial paresis, facial sweating, tachycardia, mask-like face and drowsiness.

Localization. Telencephalon; diencephalon; mesencephalon; pons; medulla oblongata.

Diagnosis. Encephalitis acuta.

Result. Slow recovery.

Case VI.—*Meningo-radiculo-myelo-encephalitic type.*

Man, between fifty and sixty years of age; from Wooster, Ohio; seen in consultation with Dr. Horace Mateer and Dr. Sydney R. Miller, March 25, 1919. Later, seen also by Dr. H. M. Thomas and others.

Complaints. Intense lancinating pains in trunk and lower extremities; constipation.

Onset. On February 19, 1919, severe backache. On February 20, patient visited relatives (three cases of influenza in the house). On February 22, he ate freely of chicken livers (suspected). On February 23, in the morning, he awoke with severe hiccough, which lasted all day. On February 24, he noticed pain and constriction (girdle) about the waist. Better during the next few days. On March 1, severe stabbing pains radiating from the left lumbar region around the groin. These grew worse for two or three days, but descended, radiating into the left lower extremity. Then he began to have pains in the right groin and the right thigh, and, later,

the pains became maximal in the right leg below the knee. On March 8, return of hiccough for three days. Temperature about 100.4°. On March 12, sudden pain in right chest and right arm; pleurisy had been suspected by a local physician and the chest was strapped after the hiccough ceased. Patient was very drowsy for four or five days, more so than the medication accounted for; "as though drunk" was the report of the nurse. Pains were chiefly cutaneous, and were worse at night.

Positive Findings on Examination. Right pupil sluggish; gait slightly unsteady; knee-jerks exaggerated; looks listless; Oppenheim + on right side.

Laboratory Tests. Blood. W. B. C., 9000; WaR = 0.

Urine. Slight albuminuria.

Cerebrospinal Fluid. March 24, clear; pressure, + +; cells, 48 = S. M.; globulin, + + +; WaR = 0.

March 31. Clear; pressure, + +; cells, 14 S. M.; globulin, + + + +; WaR = 0.

April 5. Clear; pressure, +; cells, 14 S. M.; globulin, + + + +; WaR =0.

Course in Nursing Home. Rapid improvement. Marked benefit from lumbar punctures.

Summary. Root pains in lower thoracic and lumbar segments, with extension to roots below and later to roots above; slight fever; drowsiness; hiccough; ataxia; sluggish right pupil; changes in cerebrospinal fluid.

Localization. Meninges; spinal nerve roots; spinal cord; telencephalon.

Diagnosis. Meningo-encephalo-myelo-radiculitis.

Result. Recovery.

The Clinical Phenomena of the Disease

This epidemic disease gives rise to clinical phenomena that are referable chiefly to disturbances of the functions of the nervous system. Since any area in the nervous system may be involved, with either loss of, increase of or perversion of function, and since the single cases vary greatly as to the number and distribution of areas diseased as well as to the intensity of the process in particular areas, we may, in epidemic encephalitis, meet with the greatest variety of neurological syndromes, so that it is not surprising that some clinicians, overlooking an underlying unity, have thought that several of the syndromes correspond to as many different and independent diseases. Just why the intensity of the process and the distribution of the injuries to the nervous tissues are so variable

we do not yet know, but there is good reason to believe that in this epidemic we are dealing with a single infectious agent as a cause, and that this agent attacks the central and peripheral cerebrospinal nervous system and its coverings in a widespread, though, at the same time, in a patchy or disseminated way. Under such conditions a great variety of combinations of general and focal symptoms must be expected in a series of cases. An understanding of the underlying pathological-anatomical process in epidemic encephalitis makes clinical diversity no surprise; what arouses wonder is rather the frequency with which certain associations of symptoms, such as lethargy, with fever and ophthalmoplegia, are met with in the epidemic.

Onset. This may be sudden or gradual, and with or without prodromata (asthenic lassitude, headache, vomiting). Some of the patients regard the attack as influenzal; others give a history of having had influenza a few days or a few weeks before; still others assert that they have not had influenza at all. The general encephalic symptoms may, in some cases, be the more marked at onset; in others, focal symptoms, referable to brain or spinal cord, or signs of meningeal irritation announce the presence of a nervous disease.

General Symptoms. The most striking general symptom, when it is present, is a disturbance of the general consciousness that manifests itself in a pathological drowsiness, a symptom that led von Economo to call the disease "encephalitis lethargica," and the lay press to dub it "sleeping sickness." All grades of this disturbance (apathy, dullness, somnolence, sopor, stupor, coma) may be met with, either in a single case or in a series, and either at or near the onset or later in its course. Some patients, however, do not manifest the symptom at all. In one patient of my series, who was drowsy for about a week, the tendency was attributed at first, erroneously, to the effects of codein administered for the relief of pain. Milder involvements of the general consciousness (somnolence and sopor) from which the patients can be roused and made to answer questions seem to have been more common in the epidemic than the severer disturbances (stupor and coma).

Other disturbances of the general consciousness, including mental depression, anxiety, and delirium, also frequently occur. A patient

may be drowsy in the daytime and complain of insomnia and restlessness at night.

Headache, vertigo, tachycardia and vomiting are common general symptoms. Outspoken choked disk was not present in any of the cases of my series, and judging from the reports is not met with though a slight optic neuritis may occur. Fever may or may not be present at the onset but is usually evident at some time during the course of the disease. It was slight in most of the cases I have seen, though I was impressed with the persistence of an elevation of temperature of one or two degrees, extending over a period of from one to two weeks in several of the cases. In some cases, there is marked pyrexia, 102° to 105°, lasting for from one to a few days.

Focal Symptoms. These are predominantly motor rather than sensory.

Commonest by far are bilateral nuclear and radicular paralyses of the eye muscles (of well-known type) with ptosis and ophthalmoplegia externa et interna (polioencephalitis superior acuta involving N. III, N. IV and N. VI); but pontile and bulbar nuclear and radicular paralyses with facial paralysis, dysmasesia, dysphagia, dysarthria, etc. (polioencephalitis inferior acuta involving N. V (motor), N. VII, N. IX, etc.) are also common as are symptoms pointing to paralysis of part of the extrapyramidal motor system (Parkinsonian mask; loss of the normal facial innervations accompanying the emotions). The lesions that are most frequent as causes of motor focal symptoms in epidemic encephalitis must, therefore, be located in (1) the midbrain about the aqueductus cerebri, (2) the pons and upper medulla oblongata and (3) the basal ganglia (globus pallidus?).

Less common motor disturbances in epidemic encephalitis, though they may occasionally be encountered, are monoplegias, hemiplegias, diplegias, aphasias, contractures, choreatic and athetotic disturbances of motility and general or circumscribed convulsive seizures.

Focal phenomena of a sensory nature are much less frequent than those of a motor nature above referred to. Nevertheless, sensory symptoms due to focal lesions of the sensory areas (cortex) and paths (corona radiata; lemnisci) are occasionally met with (hemi-

or mono-anesthesias; paresthesias; hyperesthesias; algias; more rarely hemianopsia). In one of my cases, in which there was a meningo-myelo-encephalitis, severe root-pains in the trunk and lower extremities were prominent.

Acute ataxias of different types (according to the localization of the lesions) may be exhibited. The commonest form is the cerebellar type, due doubtless to lesions of the cerebellum or its peduncles, or of the red-nucleus mechanisms.

Meningeal Symptoms. Only in relatively few cases are the clinical signs of an outspoken meningeal irritation present. In one case of my series, there was pain in the neck and back, some rigidity of the neck, positive Brudzinski sign and a positive Kernig sign. Von Economo, S. A. K. Wilson and others have reported similar cases. That there is a slight patchy involvement of the leptomeninges in the inflammatory process in many cases has been shown, however, by postmortem examinations and by the increased cell-count and the positive globulin reaction in the cerebrospinal fluid.

Cerebrospinal Fluid. This may, or may not, be under increased pressure. The fluid looks perfectly clear, and no film, as a rule, forms on standing. In some undoubted cases of the disease the cell-count has been normal and the globulin test negative. The apparent normality of the fluid on naked-eye examination apparently misled many of the European observers, who made the earlier reports on the disease, to declare that no changes are present in the cerebrospinal fluid Abnormal fluids have been very constantly encountered in my own cases, though they would have been overlooked had the examiner failed to make a cell-count and a globulin test because of the apparently normal microscopical appearances. *In my experience, a cell-count in the cerebrospinal fluid of from* 10 *to* 100 *small mononuclears along with a positive globulin reaction with negative Wassermann and negative bacteriological smears and cultures is at the time of an epidemic of encephalitis strong corroborative evidence of the existence of the disease in a patient in whom the process is for any other reason suspected to exist.*

Negative findings in the cerebrospinal fluid do not, however, rule out the disease.

Still another point regarding the cerebrospinal fluid is worthy of

comment. In more instances than accidental injury to a small bloodvessel will apparently account for, a bloody fluid is obtained on lumbar puncture on patients suspected to be suffering from the disease. This point has been noted also by other observers, and it seems likely that the well-known hemorrhagic tendency in the disease is thus sometimes manifested.

The Blood. A slight leukocytosis is usually present. The white cell count in my cases varied between 3058 and 17,600 per c.mm. except in one instance in which the cell count was 22,850. The differential count of the white cells usually, though not always, reveals a slight relative and absolute increase in the polymorphonuclear neutrophile elements (70 to 90 per cent. of the total white count).

The Urine. A trace of albumin and a few casts are sometimes demonstrable, doubtless due to a slight toxic-degenerative nephropathy such as is met with in most acute infectious processes. Renal function, as far as the phthalein test has been applied, appears to be unimpaired. When severer renal disease, as in chronic alcoholism, accidentally accompanies encephalitis with lethargy, the differential diagnosis may be difficult, as in one case of my series in which the delirium and coma were thought at first to be due to uremic intoxication.

Duration of the Disease. Whether the disease terminates in death or in recovery, the course may be either brief or prolonged. In severe fulminant cases death may occur in a few hours or days. In many instances, both mild and severe, recovery has been rapid, the symptoms lasting from a few days to a month. In the majority of cases, however, the disease is a protracted one, extending over many weeks and, in some instances, over several months.

Prognosis

As regards life, this is much better than might have been expected, even in cases that at onset present the gravest symptoms. The mortality has been variable in different countries, and seems to have been greatest in Austria and in France. Six out of eleven of the cases reported from Austria by von Economo died; seven of Netter's

fifteen cases reported from France were fatal; only two of S. A. K. Wilson's thirteen cases reported from London were fatal; in my own series, it happens that there have been no deaths at all, due to accidental encounter of a mild group of infections. Though just what the mortality rate has been in the United States, it is as yet difficult to estimate; Bassoe, Pothier and Tucker have all reported fatal cases, and the newspapers have given evidence of many deaths all over the country from "sleeping sickness."

As regard residues and sequelæ in the patients who recover, it is, as yet of course, too early to make any definite statement. I have been impressed, on the one hand, with the very remarkable improvement observable in some instances within a few weeks (disappearance of paralyses; recovery of facial expression and vanishing of the Parkinsonian mask; replacement of depression by normal mood), and, on the other hand, with the persistence in some cases over a long period of the eye-muscle disturbances, the dizziness, the depression, and the asthenia.

We must be on the look-out in the coming period, I believe, for sequelæ, especially, as it would seem likely that large numbers of the milder infections must have gone entirely unrecognized. I have the fear—let us hope that it is not well founded—that as a result of the epidemic we may see an increased incidence, later on, in the conditions hitherto known as "multiple sclerosis" and "idiopathic epilepsy."

Nature of the Disease

Observers had but little difficulty in determining early in this epidemic that they had to deal with an infectious or toxi-infectious process involving predominantly the cerebrospinal nervous system. The clinical phenomena of an epidemic disease (of acute onset with fever) that manifested itself by a disturbance of the general consciousness and by paralyses especially in the domain of the upper, and sometimes of the lower, cerebral nerves left no doubt on this point, but had there been any doubt it would soon have been dissipated by the necropsy findings, which revealed lesions of an inflammatory, and sometimes of a hemorrhagic, character disseminated throughout the nervous system and its coverings (encephalitis;

encephalomyelitis; meningo-encephalo-myelo-neuritis). The resemblance of the clinical features in single cases to various well-known and less well-known syndromes (Wernicke's "polioencephalitis superior acuta;" Strümpell's "primary acute encephalitis;" Wickman's "encephalitic form of the Heine-Medin disease;" Leichtenstern's "post-influenzal encephalitis;" acute infectious polyneuritis; botulism with ophthalmoplegia; the mysterious epidemic disease known as "nona" in 1890; and the epidemic "sleeping sickness" [*Schlafkrankheit*] described after a grippe epidemic in Tübingen by Camerarius as far back as 1718) was quickly detected by one or another of those who had opportunity to study the outbreak. An epidemic of an acute infectious (and inflammatory) disseminated meningo-encephalo-myelo-neuropathy closely resembling, if not identical with, certain diseases earlier described had, then, presented itself in many different countries of the world for study and for consideration.

Concerning the etiology of the disease, very different opinions have been advanced. Some investigators, especially those who studied in the first two or three areas of what is now seen to be a pandemic distribution of the disease, evidently thought that they were dealing with an entirely new malady. Thus von Economo who in Austria described it as "encephalitis lethargica," Bradford, Bashford and Wilson who studied a special group of cases in the British Expeditionary Force and designated it "acute infectious polyneuritis," and Netter who in Paris described it as "encéphalite léthargique épidémique" all seem inclined to regard it as a new disease, though they admit its resemblance to recognized diseases. It was soon seen, however, on analysis of the clinical phenomena and the pathological-histological findings, that under some one or other form of encephalitis, or of encephalo-myelitis, parallel phenomena have already been described in the medical literature. Thus most of the phenomena, both clinical and histological, will be found paralleled in the larger collective reviews of acute non-suppurative encephalitis, such as those of Chartier (1907), by Oppenheim and Cassirer (1907) and by Vogt (1912). Most of the cerebral nerve paralyses will be found duplicated in the cases of encephalitis tabulated by Wilbrand and Saenger (1900). Most if not all of the

pathological-histological findings appear to be in accord with those described by Friedmann (1890–1898), Bücklers (1892), Flatau (1900), Spielmeyer (1902), and Raymond and Cestan (1904). One of the English writers (S. A. K. Wilson) concludes that "what appears to be new is the occurrence in epidemic form of cases of encephalitis not to all appearance due to the action of a known infective or toxi-infective agent, but presenting clinical symptoms any or all of which have been noted in various kinds of encephalitis with which the neurologist has long been conversant." But is even the occurrence in epidemic form new? Have we not records of one epidemic by Camerarius in 1718, of another by Lepecq de la Cloture in 1768, of at least three mentioned by Ozanann (in his history of epidemic diseases) as occurring in 1745, in 1800 and in 1802, of an epidemic of encephalitis described by Leichtenstern after the great influenza epidemic of 1889–1890, as well as of epidemics of "nona" that occurred at about the same time (reports collected and reviewed by Longuet in 1892) ?. In England the first cases observed in the present epidemic of encephalitis were thought to be instances of meat-poisoning (botulism). The problem of etiology as at present discussed for the recent epidemic resolves itself into three questions: (1) Is the disease due to the virus that causes influenza; (2) Is the disease due to the virus that causes the Heine-Medin disease or to a modification of that virus; and (3) Is the disease due to a virus *sui generis?*

The possibility that the virus that causes influenza may also be the cause of the encephalitis recently pandemic is well worthy of serious consideration. For we have good reason to believe that encephalitis like meningitis, like pleuritis, like nephritis, and like other inflammations, may at different times be due to entirely different causative agents. Thus it is well-known that non-suppurative encephalitis may occur as a complication of scarlet fever, of measles, of chicken-pox, of whooping-cough, of pneumonia, of anthrax, of malaria, of poliomyelitis and of other infectious diseases, and it is probable that these complicating inflammations of the brain are due to local infection of the nervous system with the specific virus that causes the primary general disease, rather than that they are all instances of mixed infections of a unitary virus causing enceph-

alitis along with the specific viruses of the several infectious diseases mentioned. Now if this view be a correct one it is surely not a wholly improbable supposition to suggest that an epidemic, or a pandemic, of encephalitis occurring in association with or soon after an epidemic, or a pandemic, of influenza may be due to an encephalic localization of the influenza-virus. Indeed, the encephalitis that was described by Leichtenstern, in 1890, is generally referred to in the literature as "influenzal encephalitis," and it may be recalled that Pfuhl, and later Nauwerck in fresher material, asserted that they had demonstrated the presence of the *Bacillus influenzæ* of Pfeiffer in the diseased cerebral tissues in "influenzal encephalitis." Though the latter demonstration is at present less convincing than formerly, owing to the reopening of the question of the etiology of influenza itself and to the doubt cast upon Pfeiffer's bacillus as its cause [cf. Bloomfield (A) and Harrop (G) *et al.*], still, the occurrence of encephalitis in epidemic (and in pandemic) distribution in such close connection with epidemic (and pandemic) influenza as that observed in 1890–1892, and as that at the present time, strongly suggests at least one of the three following possibilities: (1) that the influenzal virus is the cause of the epidemic encephalitis, (2) that influenzal infection predisposes to infection with the virus of encephalitis, or (3) that the cosmic influences that determine the occurrence of epidemic influenza also determine the occurrence of epidemic encephalitis, even if each disease is due to a separate and distinct virus. It may be argued also that influenzal encephalitis tends to assume a special clinical form (acute cerebritis) but certainly other forms also occur in the epidemic; indeed in the present outbreak the poliencephalitis superior type has predominated. Granting the weight of the arguments adduced it must be admitted, however, (1) that the incidence of epidemic encephalitis is very low compared with that of influenza, (2) that the available data do not permit of the assertion of any direct parallelism of incidence and distribution in the two diseases, and (3) that some of the patients who have suffered from encephalitis deny any preceding attack of influenza though doubtless all have been exposed to that disease. Thus until we are sure of the precise nature of the virus of influenza on the one hand and of the virus of epidemic encephalitis on the

other, the questions regarding the exact etiological relationships of the two diseases must be left open.

It is but little wonder, too, that some have thought that the virus of epidemic encephalitis may be identical with, or a slight modification of, the virus (*Flexneria noguchii*) that is the cause of the Heine-Medin disease (Poliomyelitis anterior acuta). For, in the first place, since Wickman's studies, cerebral, pontile, cerebellar, bulbar and meningeal forms of the Heine-Medin disease are certainly known to occur. And in the second place the pathological-histological lesions in the central nervous system and the findings in the cerebrospinal fluid in epidemic encephalitis and in poliomylitis show a close resemblance. But against the view of identity there are many facts that may be urged. The onset of the paralyses is very different in the two diseases, since in poliomylitis the paralyses are all there from the beginning, whereas in epidemic encephalitis the paralyses begin insidiously, often as ptosis or loss of power of accommodation, and gradually extend through a period of several days or longer to other muscles. Bilateral symmetry of the paralyses is more common in encephalitis, unilateral or asymmetrical paralyses in the Heine-Medin disease. The fever is usually slight and often more marked after the paralyses have developed in encephalitis; in the Heine-Medin disease the fever is, as a rule, highest before paralysis occurs. There is a much higher leukocytosis in the blood and also a higher cell-count in the cerebrospinal fluid in the Heine-Medin disease than in encephalitis. The age-incidence is also different, since encephalitis is common at all ages of life, whereas the Heine-Medin disease shows an especial predilection for childhood and adolescence. Again, a careful study of the distribution of the cases of encephalitis and of poliomyelitis in England has shown that the two series of cases are distributed independently of one another. And, finally, if there were identity of etiology one would expect more typical encephalitis cases in epidemics of poliomyelitis and more typical poliomyelitis cases in epidemics of encephalitis than we actually see. Some investigators, though fully granting that there may not be identity of etiology, suggest that the virus of encephalitis may be one special strain and the virus of poliomyelitis another special strain of a single microörganism, just as we now recognize

Type I, Type II, and Type III, etc., of the pneumococcus, or recognize that Bacillus paratyphosus A and Bacillus paratyphosus B are two strains producing similar but not identical disease. In favor of this view may be adduced the findings of v. Wiesener of Vienna who asserts that he has isolated an organism (globoid diplococcal form) from encephalitis and reproduced the disease in monkeys, and that this virus resembles closely that isolated by Flexner and Noguchi in poliomyelitis. A similar virus seems to have been grown by Wilson from Bradford's "acute infectious polyneuritis" cases, and with this virus it was also possible to reproduce in monkeys what they believed to be the disease they had under study. It is of course possible that just as we have a group of diseases (the leishmaniases) due to different strains of species of *Leishmania*, so we may have a group of diseases (the flexneriases) due to different strains or species of an organism (*Flexneria*) of which the virus of the Heine-Medin disease is one. But until more extensive virus-studies and experiments have been made it would be unwise to look upon such a view as anything more than an interesting speculation.

That epidemic encephalitis may, finally, be due to some causative agent neither identical with, nor even a modification of, any other virus is quite possible, and is, indeed, the view held by a number of those who have studied the disease. If this view turn out to be the correct one, it will be interesting later on to find out whether the virus isolated by v. Wiesener, that isolated by Wilson, or some entirely different filtrable (or unfiltrable) virus is the etiological agent.

Therapy

The patients under my observation have evidently been of the milder type, as none of them died. Convalescence has been tedious in several of them, and in how far there will be residual phenomena in some, it is as yet too early to be sure.

At the onset of the disease, rest in bed, protection from external stimuli of all kinds, laxatives, bland diet, and relief of headache, and of pains would seem to be desirable.

In my experience, lumbar puncture, done for diagnostic reasons,

relieved the symptoms so markedly in several instances that it was repeated at intervals as a therapeutic measure.

During convalescence, prolonged rest, careful nursing, a nutritious diet and mild hydrotherapy, electrotherapy and massage have been the only measures made use of. Complete recovery without residuals seems to be common.

THE DIAGNOSIS OF LATE SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

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(ABSTRACT)

As a result of the increased use of the Wassermann test for syphilis on the blood serum a considerable number of cases of syphilis are being diagnosticated in which the original infection occurred some years before. In these cases of old syphilis in which the serum shows a positive Wassermann reaction it is assumed there are still some living sphirochetes somewhere in the body, and an attempt should be made to kill them off.

It is now generally recognized that late syphilis of the central nervous system needs special treatment, and this treatment should be started early. It is therefore important to find out where the living spirochetes are in these old cases in order to institute proper treatment.

The question arises as to whether a careful history and physical examination will reveal spirochete activity in the central nervous system or must that special diagnostic aid, the lumbar puncture, be resorted to. Although a lumbar puncture is not a dangerous procedure it is often an inconvenience to the patient, as it may force him to remain in bed for several days.

Since the opening of the Peter Bent Brigham Hospital considerable attention has been paid to the diagnosis and treatment of syphilis of the central nervous system. As a result, lumbar puncture has been performed on practically all cases in which even a suspicion of syphilis of the central nervous system was present. It was

thought that a study of these cases, therefore, might reveal some in which there were practically no signs or symptoms referable to the central nervous system, and yet the spinal fluid examination would indicate syphilis.

Two hundred and thirty-three cases were studied. The hospital diagnoses were used and the cases grouped as tabes, general paresis, syphilis of the meninges and cerebrospinal syphilis. The history and physical examination as recorded by the house officer on admission were used. It was felt that this examination represented as good an examination as the average patient would receive in a general hospital or an out-patient department.

In each group, except that of syphilitic meningitis, there was a definite small percentage of cases, between 2 per cent. and 5 per cent., in which neither the history nor physical examination called the attention of the examiner to the central nervous system, even after syphilis was known to be present. These cases would have been missed as cases of syphilis of the central nervous system if for one reason or another the lumbar puncture had not been performed. If this number will be missed in the cases studied carefully in the wards the opportunity of overlooking cases in the outdoor departments, where examinations are made under more trying conditions, is all the better.

Therefore, since the lumbar puncture is not dangerous, and since it may expose syphilis of the central nervous system in which physical examination has failed to do so, and since a definite diagnosis is desired early in order to institute appropriate treatment, it seems fair to demand a lumbar puncture in all cases of old syphilis before beginning treatment.

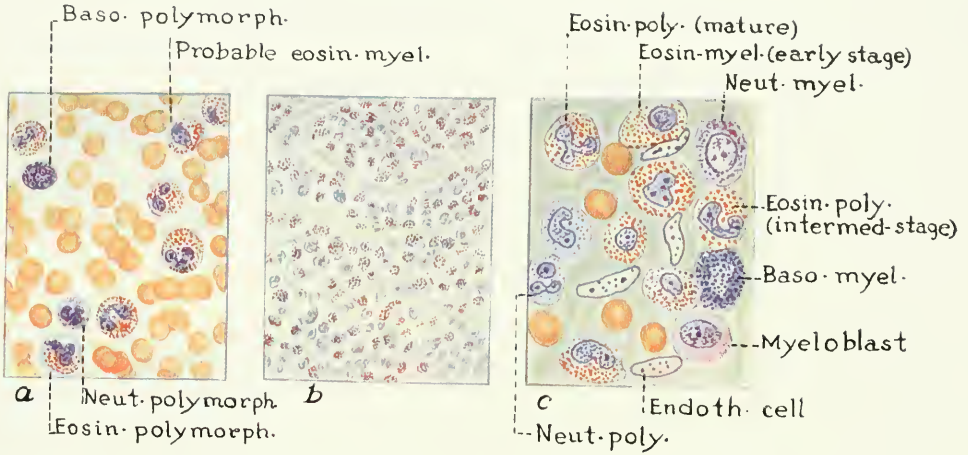

Fig. 1.—Drawings of Actual Fields to Show Eosinophils.

a. Eosinophils in the blood stream, observed with 10 X ocular and ½ immersion oil objective.

b. Bone-marrow cells showing remarkable predominance of eosinophilic myelocytes, ⅙ objective, 10 X ocular.

c. Bone-marrow under ½ immersion oil objective and 10 X ocular.

PERSISTENT EOSINOPHILIA WITH HYPERLEUKOCYTOSIS AND SPLENOMEGALY

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As the basis for a discussion of eosinophilia I wish to review a case which seems to be unique in medical literature: eosinophilic hyperleukocytosis associated with marked splenomegaly and moderate glandular enlargement. This case suggests a consideration of (1) the origin and function of the eosinophils, (2) the clinical incidence of eosinophilia, (3) the occurrence of eosinophilia with hyperleukocytosis, and (4) the possibility of the existence of an actual eosinophilic leukemia, apparently following splenectomy in a case of eosinophilic hyperleukocytosis.

Case 81201.—*F. H., male, aged thirty-one years. Marked splenomegaly. Slight enlargement of superficial lymphatic glands. Leukocytosis* 21,800 *before splenectomy, with an eosinophilia of* 73.6 *per cent. Splenectomy July* 15, 1914. *Weight of spleen* 2110 *gm. Macroscopic appearance of spleen similar to that of myelogenous leukemia. Rapid increase of leukocyte count to* 97,200 *and later to* 211,000, *eosinophilia from* 79 *to* 90.7 *per cent. Good general condition for period of four years following splenectomy. Death January* 19, 1919, *of empyema following pneumonia. Necropsy: Enormous numbers of eosinophilic polymorphonuclears in all hemopoietic organs. Eosinophilic myelocytes numerous in lymph glands, spleen and bone-marrow. Obliterative pericarditis and fibrous perihepatitis.*

March 11, 1913, a man, aged thirty-one years, with generalized anasarca and moderate anemia, presented himself for examination. His family history was negative. He had had a continuous fever, with the characteristics of typhoid fever, eight years previously, and this had been followed by pneumonia. Convalescence from this

severe illness was protracted and the patient had not since that time entirely regained his former strength. Eighteen months before the examination he developed moderate dyspnea and a cough; he had an occasional attack of vomiting and some wheezing, but did not have a typical paroxysmal asthma. Thirteen months before, he had been much annoyed by a severe recurrent pain in the left thoracic region; this, in the light of later findings, may have been due either to a pericarditis, a pleurisy, or to a perisplenitis. Ten months before examination a transitory edema of the legs and face developed, which would disappear during the night. Five weeks previous to examination the patient became quite ill with cough, shortness of breath and wheezing, without chill or fever. He could not work, but was not confined to bed. Three weeks before examination he began to suffer from a moderately severe pain at the right costal margin, associated with vomiting and questionable jaundice. One week before examination a generalized edema developed and became progressively worse.

The general physical examination showed a marked superficial edema of the legs and body up to the level of the arm-pits. The scrotum was edematous; evidence of ascites was present, the liver and spleen were enlarged, and the axillary glands were easily palpable. There was no definite evidence of lues and the Wassermann test was negative. There was no indication of nephritis. The acute condition at that time seemed to be due to either a myocardial insufficiency or a cirrhosis of the liver.

The most interesting finding, however, was the presence of eosinophilia of 66.3 per cent. (Table I). The leukocyte count at the time of the first examination in March, 1913, was 15,400; the total lymphocyte count was 19.3 per cent. while the polymorphonuclear count was only 13 per cent. The anemia itself was of a secondary type, with a red cell count of 3,620,000 and a hemoglobin of 69 per cent. On account of the extremely high eosinophilia a very careful search for parasites was made. The stools were repeatedly negative and a microscopic examination of skeletal muscle was negative.

A lymph gland removed from the axilla for microscopic examination showed a moderate inflammatory reaction. The germ centers were intact; a marked endothelial hyperplasia was present. Eosino-

philic polymorphonuclear leukocytes were quite numerous and a few scattered eosinophilic myelocytes were found.

The patient was placed at absolute rest in bed on a milk diet; his edema practically disappeared within ten days. The spleen was then easily outlined and was found to extend to the navel and to the level of the left iliac spine. Two months later the patient was able to do light work. During the summer and fall of 1913 he worked moderately hard and quite regularly. In June, 1914, more than one year after the original examination, the patient's general condition was fairly good. His anemia, however, was quite definite; the red cell count was 3,500,000, the eosinophil percentage was 75.4, while the total leukocyte count was 13,800.

TABLE I.—BLOOD COUNTS (CASE 81,201, F. H.).

Date	Mar. 11, 1913.	Dec. 16, 1913.	July 14, 1914.	Splenectomy, July 15, 1914	Aug. 5, 1914.	Nov. 24, 1914.	May 25, 1915.	Dec. 5, 1916.	May 15, 1917.	Oct. 10, 1917.	Nov. 26, 1918.
Hemoglobin	69	80	75		68	85	70	69	52	58	50
Red blood cells (millions)	3.62	4.16	3.86		4.02	4.60	3.56	4.25	3.48	3.62	2.72
White blood cells	15,400	15,400	21,800		97,200	133,000	208,000	103,000	211,000	135,000	81,800
Small lymphocytes	18.3	16.0	9.6		6.8	11.3	5.0	9.0	3.7	5.3	5.0
Large lymphocytes	1.0	4.8	6.0		1.2	1.3	4.2	0.3	1.0	2.0	1.7
Polymorphonuclears	13.0	19.4	9.8		12.4	10.0	6.8	6.7	4.3	5.7	7.0
Eosinophils	66.3	57.6	73.6		79.0	75.0	83.4	83.0	90.7	87.0	84.0
Basophils	1.3	2.2	1.0		0.6	2.3	0.4	..	0.3	..	0.7
Neutrophilic myelocytes	..	..	..		..	..	..	0.3			
Eosinophilic myelocytes	..	..	..		..	..	0.2	..	..	..	0.7
Normoblasts	..	..	..		..	..	1.	1.	..	..	1.

In view of the persistence of a chronic anemia of the secondary type and the presence of a marked splenomegaly, splenectomy was decided. The operation was performed July 15, 1914, by W. J. Mayo. The spleen was very large, measuring approximately 10 inches by 12 inches, and weighing 2110 gm. Extensive perisplenitis was present and the organ was almost completely adherent to the vault of the diaphragm, to the wall of the stomach, and to the parietal peritoneum. Macroscopically it had the appearance of the spleen in myeloid leukemia. The liver, especially the left lobe, was very large. A small amount of abdominal fluid was present. The gall-bladder was distended, but gall-stones were not palpable.

Splenectomy was followed by a gradual and steady improvement,

especially with respect to the patient's strength and general condition. Within one month after splenectomy, however, the leukocytes had risen from 21,800 to 97,200, 79 per cent. of which were eosinophils.

During the fall of 1914 the patient felt better than for seven or eight years. His weight was 159 pounds and he was able to do light work. The liver remained enlarged and in November, 1914,

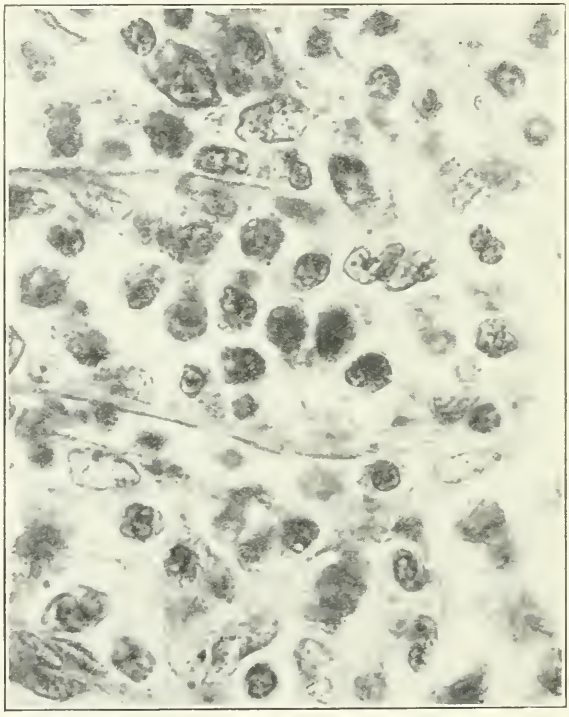

FIG. 2.—Microphotograph of spleen, showing eosinophilic polymorphonuclear leukocytes and myelocytes. They are not so plain in the spleen as they are in the lymph gland (Fig. 5), due to poor fixation.

it extended three finger-breadths below the costal margin. The superficial glands in the neck and axilla were easily palpable. During 1915 the patient's general condition was quite satisfactory, aside from slight shortness of breath on exertion. During the winter of 1916 there was a slight increase in the size of the liver and a superficial edema was occasionally present, but by summer the

patient was so improved that he was able to do regular farm work. A pruritus of indeterminate type developed; this may have been an expression of the patient's chronic toxemia. In 1917 the patient's general condition was quite satisfactory except for occasional attacks of pruritus and of moderate dyspnea and edema. October 10, 1917, the leukocytes numbered 135,000, 87 per cent. of which were eosinophils. The patient continued to be in fairly good health until October, 1918, at which time a gradually increasing

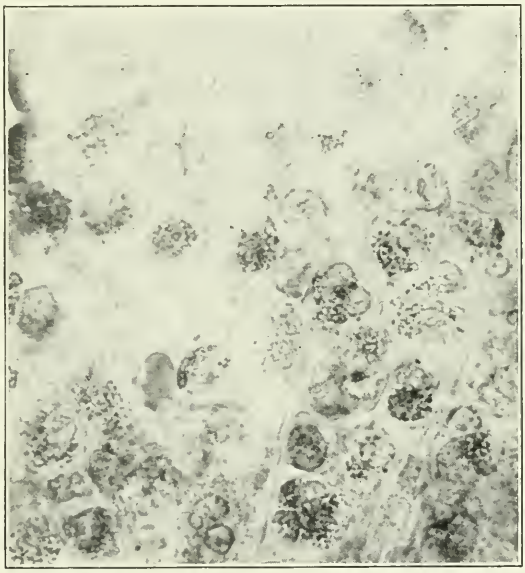

FIG. 3.—Microphotograph of bone marrow, showing numerous eosinophilic polymorphonuclear leukocytes and a few eosinophilic myeloeytes. The coarse granules, often clumped at one side of the cell, are prominent. 10X ocular, $\frac{1}{12}$ objective, Jenner stain.

weakness, dyspnea, and cough developed, later associated with an acute illness, which probably was pneumonia, as our examination in November, 1918, revealed evidences of unresolved pneumonia, and a roentgen-ray examination of the chest showed an infiltration in the region of the right middle lobe, together with a considerable enlargement of the cardiac shadow. The patient was anemic, the hemoglobin being 50 per cent. and the red cells 2,720,000. The patient was advised to have hospital care and observation, but this

was refused; one month later he returned in a very bad condition. There was then evidence of fluid in the right pleural cavity. A catheter was inserted through a cannula and 1300 c.c. of yellow pus were aspirated. A culture showed pneumococci. Through an oversight a cellular and chemical study of the pus was not made. The pleural cavity was treated with Dakin solution. The patient's

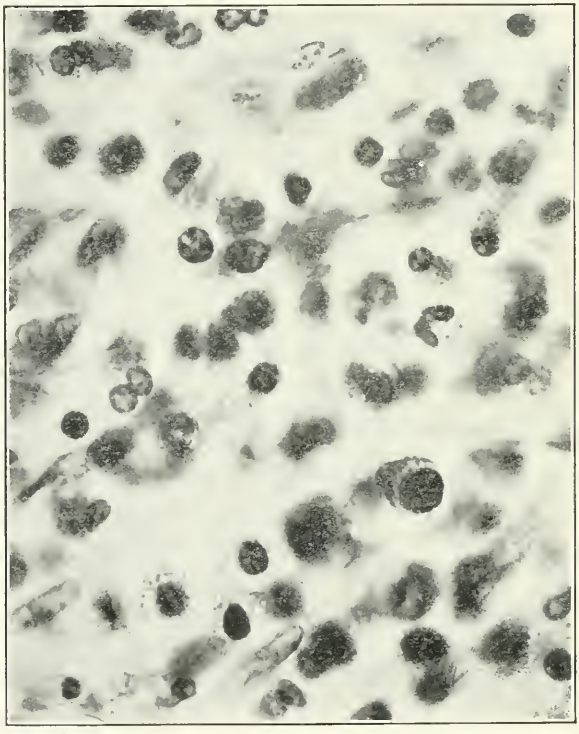

FIG. 4.—Microphotograph of bone-marrow, showing eosinophilic myelocytes and polymorphonuclear leukocytes.

general condition was not satisfactory after the development of empyema, and on January 18, 1919, his temperature rose rather suddenly to 102°; he died January 19, 1919, probably as the direct result of bronchopneumonia.

Cytology of Blood Smears. A study of the blood smears revealed that almost all the eosinophils were of mature type and differed only

slightly from the eosinophilic polymorphonuclears which are ordinarily found in the blood stream. These cells were somewhat larger than usual and the number of nuclear lobes was increased. Many cells had three lobes. The protoplasm seemed to be basophilic rather than neutrophilic and a considerable vacuolation was present

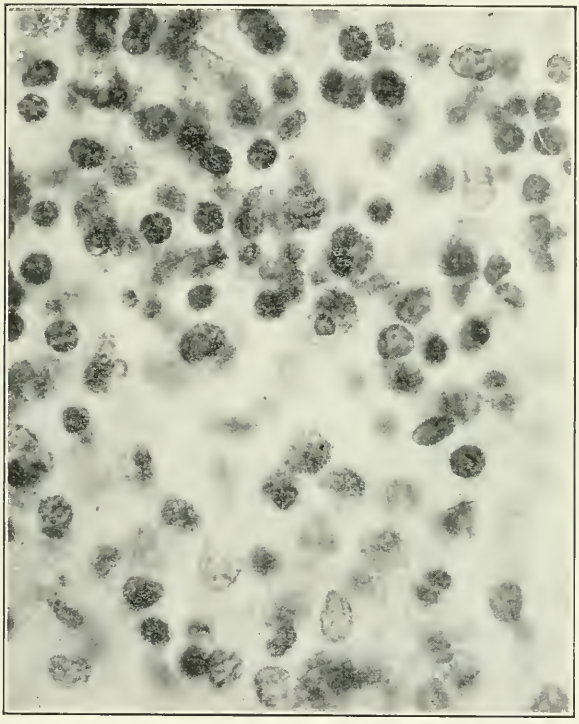

FIG. 5.—Microphotograph of large lymph gland near the head of the pancreas, showing numerous eosinophilic polymorphonuclear leukocytes and a few eosinophilic myelocytes.

while a few cells were ruptured. Certain eosinophils were to be seen in which a few small basophilic granules were present and an occasional eosinophil had the appearance of a transitional cell or metamyelocyte with a horseshoe nucleus. Rarely, however, was it possible to discover a true eosinophilic myelocyte in the blood smears (Fig. 1*a*).

Examination of the Spleen Removed at Operation July 15, 1914.* The spleen, weighing 2110 gm., was approximately 10 by 12 inches. The Malpighian bodies were intact though not numerous. Cellular hyperplasia was marked, eosinophilic polymorphonuclears were very numerous and a few eosinophilic and neutrophilic myelocytes were seen. The increase in the amount of fibrous tissue was only slight (Fig. 1). The myelocytes were much less numerous in the spleen, which was removed in 1914, than they were in the glands removed at necropsy four and one-half years later.

Examination of the Bone-marrow (Postmortem January 19, 1919). The bone-marrow was hyperplastic and contained great numbers of eosinophilic polymorphonuclear leukocytes; the majority of them were in a well-developed stage while a few were apparently of intermediate type. Eosinophilic myelocytes were present in the proportion of 3 to 10 in favor of eosinophilic polymorphonuclears. An occasional neutrophilic polymorphonuclear and, very rarely, a basophilic myelocyte could be found. The erythrogenic function of the bone-marrow seemed to be almost in complete abeyance (Figs. 1*b* and *c*, and 3 and 4).

*Examination of the Lymph Gland from the Region of the Head of the Pancreas.** The gland was about 3 cm. in diameter. The germ centers were intact. Eosinophilic polymorphonuclears were very numerous. A few scattered eosinophilic myelocytes and neutrophilic myelocytes were found. The eosinophilic myelocytes occurred in the proportion of 1 to 10 in favor of the eosinophilic polymorphonuclears. The eosinophilic polymorphonuclears showed chiefly fully developed forms and occasionally intermediate forms. The eosinophilic polymorphonuclears were almost as numerous as the lymphocytes (Fig. 5).

Anatomic Diagnosis. Right bronchopneumonia; right fibrous pleuritis; obliterative pericarditis; fibrous perihepatitis; cirrhosis of the liver; general lymphoid hyperplasia. The obliterative pericarditis and the fibrous perihepatitis were probably of long standing and much of the symptomatology during the last six years of the patient's life could be attributed to cardiac and hepatic disease. While these latter pathologic conditions were apparently of a

* Examination of tissues was made by A. C. Broders.

chronic nature the cirrhosis of the liver was of mild grade and of mixed type, but a generalized fibrous peritonitis, commonly seen in Pick's or Concato's disease, was not present.

Discussion

1. *The Origin and Function of the Eosinophils.* Most hematologists subscribe to the heteroplastic theory of the formation of granular cells, at the same time admitting the occurrence of mitosis and the homoplastic origin of a certain number of these cells. They agree that eosinophilic polymorphonuclear leukocytes develop chiefly from undifferentiated mononuclear cells within the bone-marrow, and in smaller numbers within certain special tissues of the organism, particularly lymphoid tissue. Whether this development is a direct transformation from lymphocytes or is the result of maturation from metastatic bone-marrow tissue is undecided. In the case herewith reported the presence of eosinophilic myelocytes and immature forms of eosinophilic polymorphonuclears in the spleen and lymph glands indicates quite clearly either a normal or a perverted production of eosinophils within these organs. There is no conclusive evidence in favor of the theory of the direct transformation of neutrophilic polymorphonuclears into eosinophils either in the blood stream or in the general tissues. The theory of the origin of eosinophilic granules from hemoglobin or its dissociation products is strongly advocated by Weidenreich. The recent work of Downey shows that in the bone-marrow of the adult guinea pig eosinophilic granules are differentiated gradually from a basophilic protoplasm and that their progressive evolution is marked by complex changes in staining reactions, size, and shape, and also that there is a direct transformation from basophilic to oxyphilic granules. The complex evolution of the granules indicates that they are true endogenous formations. The granules of eosinophils even in the younger cells and before they become clearly oxyphilic can be differentiated from the granules of mast cells by their size, shape, and staining characteristics. Downey explains that there need be no conflict between his own conclusions concerning the endogenous origin of eosinophil granules in the bone-marrow and Weidenreich's demonstration of an exogenous

origin as a result of phagocytic activity. This can be explained on the basis of Gütig's theory that two types of eosinophils exist and that, morphologically, they are distinguishable.

Very few facts concerning the function of eosinophils are known. Complete withdrawal of food is followed by a decrease of eosinophils in the peripheral circulation. There is a relationship between nutrition and the production and circulation of eosinophils, and disturbances of nutrition affect the multiplication of eosinophils more readily than that of the finely granular leukocytes (Opie). Schwarz believes that there are indications of a very close relationship between eosinophils and intestinal secretion and that possibly these cells may convey a hormone which is important for proper cellular activity in the intestine. Falta and his co-workers call attention to the fact that pilocarpin and pituitrin, substances which raise the tonus of the autonomic nervous system, also produce eosinophilia.

Lepsky concludes that eosinophilia is, in some measure, a reaction of the organism against the penetration of foreign proteins. Weinberg and Séguin, in 1915, confirmed the work of Mesnil and others by demonstrating that eosinophils possess important phagocytic properties with respect to both bacteria and cells; they also showed by the use of hydatid fluid that eosinophils are well adapted to the absorption of toxic products. In their experiments those eosinophils which had absorbed toxic material lost their phagocytic properties while these properties were retained by the neutrophilic and mononuclear cells and the hydatid liquid itself lost its antigenic power. Fiessinger recently has shown that there is a definite antitoxic leukocytic reaction and defense against the foreign proteins formed in war wounds as the result of infection and the destruction of tissue and that eosinophils are concerned in the mechanism of this defense. All of these observations lead to the conclusion that eosinophils may play a very important rôle in the maintenance of immunity.

2. *The Clinical Incidence of Eosinophilia.* Eosinophilia has been described in association with many conditions, although in most of them the percentage is neither high nor persistent. A low grade of eosinophilia is found in some cases of scarlet fever, neurasthenia, and polycythemia. A constant slight relative and marked absolute

eosinophilia is present in myelogenous leukemia. Eosinophilia also is associated with the presence of parasites and its occurrence in asthma and in certain cutaneous diseases is well established. The most marked eosinophilias which I have been able to find reported in medical literature have occurred in cases of trichinosis, in which the eosinophilia is transient, of lymphadenoma, especially associated with cutaneous lesions, and occasionally in cases of carcinoma and sarcoma. Reports of instances in which the eosinophils have even temporarily reached 25 per cent. or more are exceedingly rare. I have had under observation a patient (Case 104259) with Hodgkin's disease who had an eosinophilia of 33.3 per cent. with a leukocyte count of 12,000. The diagnosis was made after the excision of a gland for microscopic examination. No reason for the marked eosinophilia could be discovered. Aubertin and Giroux describe a cardiac case with cyanosis and frequent attacks of decompensation in which a persistent and very high eosinophilia was present. The leukocyte count varied from 6,900 to 13,500 and the eosinophils from 57 to 68.25 per cent. Dunger reports a case of probable carcinoma of the colon in which the leukocyte count was 35,330, 60 per cent. of which were eosinophils. Sibley reports an eosinophilia of 39.6 per cent. and a leukocyte count of 28,150 in a case of lymphadenoma associated with cutaneous lesions.

In none of these cases was a markedly enlarged spleen present; in only one instance was the eosinophilia persistent.

3. *The Occurrence of Eosinophilia with Hyperleukocytosis.* After a careful study of the literature only three instances of eosinophilia associated with hyperleukocytosis have been found. Glanzmann describes a case of lymphadenoma as "lymphatic endotheliomatosis" in which the leukocyte count varied from 12,000 to 183,000 and the eosinophils from 4 to 33.6 per cent. Reinbach reports a lymphosarcoma of the cervical region with a leukocytosis of 120,000 and an eosinophilia of 48.28 per cent. The leukocytosis was transient and the eosinophilia fluctuating in these two cases. Stillman, in 1912, reported to the New York Academy of Medicine a case of persistent eosinophilia with hyperleukocytosis and splenomegaly. The features of Stillman's case conform closely to those of the case herewith reported, and it is the only similar case that I found in the

literature. The leukocyte count varied from 118,000 to 165,000 and the eosinophils from 85.8 per cent. to 91 per cent. The spleen was slightly enlarged and the lymph nodes were palpable. The patient was under observation for a short time only and his subsequent record is unknown.

4. *The Possibility of the Existence of an Actual Eosinophilic Leukemia.* Our knowledge of eosinophilia in general strongly favors the conclusion that an eosinophilic hyperleukocytosis is not a true leukemia. The occurrence of eosinophilia has so far been most satisfactorily explained on the basis of the chemotactic theory. In cases of a very chronic type of toxemia or infection it is possible that certain poisons which are effective throughout the entire organism for years may induce a persistent eosinophilia of almost any degree. It has been repeatedly demonstrated that some substances may call forth a local eosinophilia which will have no recognizable effect on the blood count. When the process is more extensive and the chemical irritant affects larger parts of the organism, or possibly when a different form of toxin is circulating, the demand for increasing numbers of eosinophils, as well as the toxin itself, may react as a physiologic stimulant to the production of eosinophils in the bone-marrow and in other hemopoietic structures. A perversion of these tissues may be the result.

In the case which has been reviewed those conditions which may be said to argue in favor of the existence of a true eosinophilic leukemia following splenectomy are as follows: (*a*) The persistently high leukocyte count, (*b*) the marked splenomegaly, (*c*) the general glandular hyperplasia, (*d*) the gross appearance of the glands, spleen, and bone-marrow, (*e*) the occurrence of a small percentage of immature cells and an occasional myelocyte in the blood smears, and (*f*) the presence of active hyperplasia in glands, spleen, and bone-marrow, together with the presence in these tissues of numerous eosinophilic myelocytes.

The facts which constitute the evidence against the existence of an actual leukemia are: (*a*) The marked predominance of mature and almost mature eosinophils in the blood stream and in the hemopoietic system, (*b*) the postmortem demonstration of an obliterative endocarditis, perihepatitis, and hepatic cirrhosis, which would

account for a greater part of the symptomatology during the entire course of the disease and would indicate the probable presence of a chronic toxemia, (*c*) the absence of hyperleukocytosis before splenectomy, (*d*) the long duration of the disease, approximately seven years, and (*e*) the absence of the typical microscopic characteristics of leukemia.

While not entirely discarding the view that an eosinophilic leukemia may have been present at least after splenectomy, I am inclined to regard the case as an instance of eosinophilic hyperleukocytosis, the blood picture of which was remarkably altered by splenectomy. This permanent increase of the leukocytes following splenectomy for a period of four and one-half years considered in connection with the occurrence of a more or less constant eosinophilia after splenectomy for various other conditions, may be indicative of some special function of the spleen with respect to eosinophilic cells or with respect to the toxins which eosinophilic cells are capable of absorbing.

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DISCUSSION

Dr. Emanuel Libman said that he believed that Dr. Giffin's case should be called a leukemia. A similar case had recently been reported by Dr. Louis Shapiro, of Paterson, N. J., at a meeting of the New York Pathological Society.

It was interesting to note that in the case described by Dr. Shapiro, as well as in the case described by Dr. Giffin, prominent symptoms were general edema and ascites. It might prove that these are characteristic symptoms of the disease. The tendency to edema could not be explained by the presence of the eosinophilic cells, because in trichinosis the edema usually occurs early and not late when the eosinophils are very much more abundant.

In the opinion of the speaker, the splenectomy in Dr. Giffin's case had no relation to the course of the disease, because in Dr. Shapiro's case the early clinical course was exactly the same as in Dr. Giffin's case, and no splenectomy had been performed.

Dr. Shapiro had the opportunity of examining the bone marrow in his case, and in it had found a very marked proliferation of eosinophilic cells.

A LONG DURATION OF REMISSION IN PERNICIOUS ANEMIA

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In his article on pernicious anemia in Osler's *Modern Medicine*, Richard C. Cabot recounts two cases having a remission lasting four years and a doubtful instance of six years. This author also has records of 37 long cases, that is, continuing more than four years. Three of these lived fourteen years. This list includes 6 cases which Cabot considers as definitely recovered.

I have to report a case first seen in 1899. It was in all respects a typical case, as the accompanying report of the blood count indicates.

Date	October 11, 1900
No. of red corpuscles per cm.	1,021,300
No. of white corpuscles per cm.	3,250
Per cent. hemoglobin (Dare)	26
Color index	1.3

Red cells.	White cells.		
Normoblasts, none	Polynuclears	60	per cent.
Intermediates, none	Small lymphocytes	34	"
Megaloblasts, two	Large lymphocytes	4	"
Microblasts, none	Transitional	0	"
Poikilocytes, large number	Eosinophiles	1	"
Microcytes, large number	Basophiles	0	"
Macrocytes, none	Myelocytes	1	"
Stippling, absent	Eosinophilic myelocytes	0	"

There was an irregular improvement for six years, at which time, although there was a moderate anemia, the blood lost all characteristics of the pernicious type. To convey some idea of the course of the case during the earlier years, the counts of the erythrocytes are given in order. The other characteristics of the blood kept in close ratio with the red count.

	Erythrocytes.	Hemoglobin.
December, 1899	2,444,000	60 per cent.
April, 1900	3,240,000	80 "
October, 1900	1,021,300	26 "
March, 1901	3,280,000	75 "
July, 1901	4,624,000	83 "
October, 1901	4,208,000	89 "
July, 1902	3,354,600	75 "
October, 1902	3,960,000	89 "
December, 1902	3,906,400	89 "
March, 1903	4,176,000	92 "
October, 1903	3,716,000	80 "
May, 1904	3,920,000	85 "
January, 1904	4,000,000	89 "
January, 1905	4,208,000	92 "
July, 1906	3,900,000	88 "
November, 1906	4,100,000	81 "
January, 1907	4,856,000	80 "

In 1907 there were no abnormal cells found. The blood was in every way satisfactory except that the polynuclears were only 53 per cent. and the eosinophiles 3 per cent.

As the patient was now discharged, and, although seen occasionally, never examined as to her blood, it is impossible to state the precise condition during the intervening years. However, from 1907 until the beginning of 1918 the patient was considered to be well.

Then there was a sharp recurrence which soon became threatening. The case failed to respond to the action of atoxyl and sodium cacodylate, which drugs formerly had appeared to be of benefit. In February, 1918, the blood count was as follows:

No. of red corpuscles per cm.	1,656,000
No. of white corpuscles per cm.	2,700
Per cent. hemoglobin (Dare)	28 per cent.
Color index	0.8

Red cells.	White cells.	
Normoblasts, 6 in 200 cells	Polynuclears	36.5 per cent.
Intermediates, 1 in 200 cells	Small lymphocytes	58.5 "
Megaloblasts, none found	Large lymphocytes	0.5 "
Microblasts, none found	Transitional	0.0 "
Poikilocytes, many	Eosinophiles	4.5 "
Microcytes, many	Basophiles	0.0 "
Macrocytes, great many	Myelocytes	0.0 "
Stippling, present	Eosinophilic myelocytes	0.0 "
Polychromatophilia, present		

Note: (Four days before transfusion.)

A transfusion of 900 c.c. from the vein of her daughter led to temporary improvement, the count rising to erythrocytes, 3,408,000;

leukocytes, 3000. The gain was transient. A fortnight later the family physician, Dr. Hall, of Bradford, Pa., reported the blood count back where it was before transfusion. A week thereafter the patient developed lobar pneumonia and died three days later, nearly twenty years from the recognition of her first attack of pernicious anemia.

This seems to show that although a patient may escape all signs of the disease (save one) for a period of ten or twelve years, yet the disease may recur.

I emphasize that there was the disappearance of all evidence of the disease save one. That one was the continuance of achylia gastrica. In a long series of cases, private and hospital, studied during thirty years I have not found an exception to the rule of the presence, sooner or later, of achylia gastrica. In this series of cases there have been several long remissions, but never has the gastric function been restored.

This persistence of achylia gastrica may have more significance than has been accorded it in late years. If we grant that pernicious anemia is the expression of an infection it is not improbable that gastric infection is in some way a link in the chain.

The belief prevails that an exceptional case of pernicious anemia goes on to recovery. Has anyone ever reported the restoration of normal gastric secretion? In view of the fact that in this case, so far as I know the most promising on record, the disease recurred twenty years after its inception and after having a remission in which there was to all appearances good health for a period of twelve years, I feel that it may be concluded that a patient probably never entirely recovers from pernicious anemia.

The persistence of the gastric lesion points to a close pathological relation between the stomach and the anemia. In this connection attention is called to the observations of Seyderhelm,[1] [2] of Strassburg,

[1] Seyderhelm, K. R., and Seyderhelm, R.: Die Ursache der perniziösen Anämie der Pferde, Arch. f. exper. Pathol. u. Pharmakol., lxxvi, 149; Wesen, Ursache und Therapie der perniziösen Anämie der Pferde, Arch. f. Wissensch. u. prakt. Tierheilkunde, 1914, 41; Experimentelle Untersuchungen über die Ursache der perniziösen Anämie der Pferde, Berl. tierärztl. Wchnschr., 1914, No. 34. Seyderhelm, R.: XVII Tagung der Deutsch. path. Gesellsch., 1914.

[2] Seyderhelm, R.: Ueber die Eigenschaften und Wirkung des Œstrius und seine Beziehung zur perniziösen Anämie der Pferde, Arch. f. exper. Path. u. Pharmakol., 1918, lxxxii, 253.

working with larvæ of the fly, Œstrus equi, occurring in the gastric mucosa of horses suffering from a severe anemia, in its characteristics said to be suggestive of pernicious anemia in man. The bibliography of this work, copied from the *Journal of the American Medical Association,* No. 9, vol. lxxii, is here attached.

DISCUSSION

Dr. Julius Friedenwald stated that in a series of 57 cases of pernicious anemia examined by him the gastric analyses were entirely in accord with Dr. Stockton's findings, that is, in the very largest number of cases there is a true achylia (74 per cent. of cases) and even during the periods of remission the gastric secretion does not return. In a smaller proportion of cases (19 per cent.) there is a marked diminution in the secretion, and in a few instances (about 7 per cent.) it remains normal.

EXPERIMENTAL STREPTOCOCCUS EMPYEMA: POSSIBILITIES OF ITS PREVENTION AND CURE BY SPECIFIC MEANS

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Streptococcus immunity remains one of the perennial problems of the infectious diseases. Much labor and thought have been expended in testing experimentally, both in animals and in human beings, the possibilities of vaccine prophylaxis and of vaccine and serum therapy in infections due to this microörganism. The results have, in a few specialized instances, seemed encouraging, but in the last analysis no assurance can at present be given for combating the streptococcus by the specific methods of immunology.

Some, at least, of the reasons for our failure hitherto to influence any one of the manifold manifestations of this microörganism are now more apparent. An active immunity of any considerable grade by means of streptococcus vaccine is difficult to induce and, secondly, it has become certain that the individual varieties or types of this rather commonly distributed pathogen are far more numerous than had been anticipated.

Army experience of the past three years has brought to our attention more vividly than ever before the very deadly effect of the streptococcus, and has stimulated many of us to renewed attempts to get to the bottom of this elusive and discouraging problem. The rapidly mobilized army of bacteriologists that has arisen in connection with our participation in the war has added many valuable facts concerning the distribution of the streptococcus in human infections, and particularly its relation to the severe forms of bronchopneumonia and empyema which occurred in enormous

numbers, both spontaneously and as a sequel to measles and influenza.

It is from the interesting observations of Cole and MacCallum, at Fort Sam Houston, on streptococcus empyema, that my own work took its point of departure over a year ago. Since that time much progress has been made in the epidemiology, bacteriology and surgical treatment of this disease. Several suggestions have also been made as to the possibility of its treatment or prevention by the use of vaccine or serum, but they have been, so far as I am aware, arrows shot into the air and based on an indiscriminating optimism derived from the common knowledge of results in infections due to other bacteria. It is almost certain from the intricacies of the problem that no practical results have been or could have been reached in this brief period.

We had known that the streptococcus could at least be divided into hemolytic and non-hemolytic varieties; it is the former particularly that is concerned in the severer pathological processes. Further differentiation on the basis of sugar fermentation in the hands of Holman and others led to the separation of several varieties of the hemolytic group. So far as I am aware—and at least so far as I have dealt with them—the streptococci from cases of human empyema would be classified by Holman as Streptococcus pyogenes. As you will doubtless learn from the following paper the classification is by no means as simple as this. And, of course, a further subdivision of the Streptococcus pyogenes on the basis of immunity tests will still further complicate the final possibilities of specific therapy as in the case of pneumococcus infections. Fortunately, for my own peace of mind, and for your assurance, I may say, at this point, that my own studies have from the beginning dealt with a single strain of the empyema streptococcus repeatedly isolated from a single colony.

This pure strain of empyema hemolytic streptococcus has been grown ever since it came into our hands in two different media on which it flourished, a 5 per cent. rabbit serum broth (pH reaction 7.2) and a 1 per cent. dextrose broth of the same reaction. Its growth in twenty-four hours is uniformly turbid on the serum medium and profuse in both culture fluids. The serum broth culture

was at first fatal for rabbits in moderate doses of 2 to 3 c.c. when injected intravenously. It has since become practically non-pathogenic by the circulatory route. When first injected into the pleura of the rabbit in relatively large doses it would produce a purulent pleurisy of irregular degree and termination. After passage through the pleura of six or seven rabbits, however, it assumed a constant property. In a dose of 0.1 cm. of a twenty-four-hour serum broth culture derived from an original pleural exudate, which may be kept for weeks in the refrigerator, it will uniformly produce a characteristic syndrome. A rapid pleurisy, first serofibrinous, then purulent, then fibrinopurulent, is followed by collapse of the lung and a plastic exudate on both visceral and parietal pleura. A turbid and at times blood-stained fluid collects in a volume of from 15 to 20 cm. The process extends through the pericardium, where a purulent fibrinous pericarditis is produced, to the pleura of the opposite side. Death occurs in from four to ten days. Blood cultures are positive only in the terminal stages, although the pleural fluid is swarming with microörganisms. At death there are no other visible lesions in the body.

This syndrome resembles, in all details, the severe human cases of streptococcus empyema that I have seen. Although we have repeatedly attempted it in both normal and gassed rabbits we have never succeeded in producing a bronchopneumonia by insufflation, although this lesion usually but not invariably precedes human empyema. We have also tried to repeat these results with the passage pleural culture which now gives us the regular results described.

The pathogenicity of this pleural culture when administered by other routes is of interest. It may be given in enormous doses intravenously (for example the sediment of from 15 to 20 c.c.) without producing death or detectable lesions. It does not localize in the pleura when given intravenously. When given into the peritoneum 1 or 2 c.c. will produce no result. Larger doses (*e. g.*, 5 c.c.), however, may produce by extension the characteristic empyema, with little or no peritonitis.

So much for the experimental syndrome. It is obviously like the human disease and is subacutely fatal, thus giving us a reliable experimental disease process on which to test specific therapy. This

report is distinctly of a preliminary nature in so far as the main object of the investigation is concerned. Vaccination by killed or living cultures of the identical strain, when administered as in human practice, that is to say, in three or even five injections containing several billions total, produce not the slightest protection against the experimental empyema. As a matter of fact there is some evidence that a distinct hypersusceptibility is produced by this type of vaccination. When vaccination is pursued, however, over a period of six to eight weeks, with twelve to fifteen injections of large doses of dead and then of living culture, the animal is invariably protected. Both serum culture and dextrose culture vaccines produce the same results. It is evident then that we have no experimental basis for prophylactic vaccination of human beings against streptococcus empyema according to accepted usages; it may, indeed, be a distinctly dangerous procedure. Further investigation alone will show whether modified methods of vaccination will produce better results that might be applied to man.

As regards passive serum immunity, I have little to say as yet. The serum of the actively immunized rabbits contains at least agglutinins for the streptococcus, as may be clearly demonstrated by an appropriate but by no means usual technic. The serum will prevent empyema when injected simultaneously with the injection dose; whether it will cure in the true sense I have not as yet determined. Here again it should be reiterated that only the serum of animals that have undergone prolonged injections of vaccine will produce the slightest result. And, again, evidence of hypersusceptibility has been seen when the serum of imperfectly immunized animals was employed.

It was evident from the unfinished nature of these results that we are still far from a possible practical goal, not only since we shall have to deal with indefinite and multiple strains of the streptococcus but even in controlling the activities of a single selected variety. It is clear, however, that the indiscriminate use of unidentified streptococcus vaccines and unknown antistreptococcus serum is in the present state of knowledge worse than useless.

ANTIGENIC RELATIONSHIPS BETWEEN STRAINS OF STREPTOCOCCUS HEMOLYTICUS

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The complete biological classification of any pathogenic microorganism presents a very complex problem. The first phase of the undertaking concerns itself with the development of reliable methods for the determination of antigenic differences between members of the species and the application of these methods to the discovery of the immunological relationships between a limited number of strains purposefully selected. In this way the degree of similarity and diversity of type is shown and also the probable number of types and the proportion of classifiable to unclassifiable strains. The next step of necessity is the testing of the adequacy and universality of the information so gained by applying the tentative classification to a large number of strains of the organism obtained under what may be described as normal conditions of pathogenicity. That some sort of equilibrium has been established in nature among microörganisms that have produced disease over long periods of time is not unlikely. Indeed, evidence obtained from the study of pneumococci supports this view, although departure from the norm may occur under special conditions. After the relationships of the pathogens of the species to one another have been discovered, it then becomes important for purposes of epidemiological study to compare by the same methods the pathogenic with the saprophytic varieties. This task requires years for its completion and many difficulties and seemingly unexplainable phenomena are encountered.

In the beginning, the broader lines of differentiation must be drawn and divergent results disregarded for the time being, since if the original conception is correct most of the discrepancies disappear with the advance of knowledge.

In this paper are presented the facts so far obtained in the present study of Streptococcus hemolyticus in accordance with the plan outlined above. The strains were collected in a limited community during the course of what may be considered an epidemic of bronchopneumonia secondary to measles. Individuals, however, from all parts of the United States were passing rapidly through this community which was a center for primary training of the aviation service, so that a wider range of territory is represented than the immediate community itself. All the strains were investigated as to their cultural reactions, bile solubility, capacity to hemolyze red blood cells and to ferment the different test sugars, and as to hydrogen ion concentration limiting their growth and thus identified as accurately as possible as Streptococcus hemolyticus of the human type.

A technic was then developed for studying the immunological reactions of agglutination and protection. By the reaction of agglutination four distinct immunological types and a certain number of unclassifiable strains have been discovered among 125 strains studied. Individuals of the same type are closely related to one another immunologically and the different types can be sharply distinguished one from the other. In addition to the four types, study of the reactions of which has been completed, there are in addition two others types, investigation of which is as yet incomplete. The technic of the aglutination reaction demands great care, both as regards the handling of the organisms and the preparation of the medium for their growth. In the medium used by us a large percentage of strains has grown sufficiently diffusely to permit the preparation of stable suspensions. To what extent continuous growth in this medium has promoted the tendency to diffuseness, and whether the same percentage of freshly isolated strains will grow diffusely, we are as yet unable to say. We have found that by the immunization of sheep a highly specific agglutinating serum is obtained, but that the serum produced from rabbits is not so

specific and may show a wider range of crossing, especially in one of the types of streptococcus described. Variations in the specificity of different animal sera have been observed by students of the immunological reactions of meningococcus. In order fully to understand this phenomenon, it would be necessary to compare the specificity of immune sera produced from different species of animals by means of the method of absorption. It is not as yet possible to undertake this kind of an investigation of Streptococcus hemolyticus. The observation has been made, however, that rabbit sera showing non-specific cross-agglutination reactions in general fail to manifest corresponding cross-protection reactions.

Whenever it has been possible to raise the animal virulence of strains of Streptococcus hemolyticus the evidence obtained from the agglutination tests has been confirmed by that gained from the protection reaction. In all instances in which this has been done one reaction has corroborated the findings of the other. The performance of reliable protection tests has been made possible by the production of sufficiently high titer antistreptococcus sera and by the possibility of raising the animal virulence of a certain number of strains to a high degree. The types of Streptococcus hemolyticus have been noted as Types S 3, S 23, S 60 and S 84, from the serial numbers of the representative strains. This nomenclature is not put forth as a final one, since we realize that probably many other human types exist, to say nothing of the bovine and cheese varieties, and that the proportional distribution of the different varieties pathogenic for man may be very different from that represented by this work. Streptococcus is the largest of all pathogenic groups of bacteria and many years will be required to bring out the information necessary to the perfecting of an adequate classification.

It is of considerable interest that all the members of Type S 6 ferment mannite and that none of the members of the other groups so far encountered ferments this sugar. A few unclassifiable strains, however, have been found to be mannite fermenters.

This work has cleared up a number of points about Streptococcus hemolyticus, which have been in dispute for many years. In the first place, Streptococcus hemolyticus of human origin is not a unit type as was previously supposed, but probably consists of a number

of types, at least four of which have been definitely identified. Previous investigators have stated that freshly isolated human strains change their antigenic properties on animal passage and that the latter procedure for the development of animal virulence gives a common antigenic character to all strains. We have found no evidence to support this contention; in fact, immune sera produced with human strains that have never been passed through animals afford a high degree of protection against strains that have received many animal passages. In addition, the antigenic differences between strains of Streptococcus hemolyticus which have been passed through animals are as distinct as those between strains which have not been so passed. The types of Streptococcus hemolyticus studied have been obtained almost exclusively from the respiratory tract and from a limited source of supply, and there is some reason to believe that those which produce cellulitis, erysipelas and septicemia may be of somewhat different character. It is therefore readily seen that only a beginning has been made in the classification of Streptococcus hemolyticus, and that before the classification is complete and the relative dominance of the different pathogenic varieties determined much work must be done.

MEDICAL ASPECTS OF WOUNDS OF THE CHEST IN WAR[1]

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Introduction. The operative treatment of wounds of the chest as of wounds of other parts of the body is a duty of the surgeon requiring great technical skill, good judgment and mastery of the fundamental principles of surgery.

Chest surgery differs, however, in two important respects from most other classes of war surgery: (1) its field has been much enlarged during the war, and (2) some of the questions which arise in connection with chest cases are of a kind with which the physician is more familiar than the surgeon.

For example, it may be important in a case to know whether the dyspnea is due to a large hemothorax, pneumothorax, pulmonary edema or massive collapse of the lung; whether the circulatory disturbance can be relieved by aspiration or is due to shock or to hemorrhage; whether the temperature is probably caused by infection of the hemothorax or due to some other cause.

The physician's experience in chest examination is helpful, and, what is even more important in times of stress, while the surgeon is constantly occupied in the operating room the physician has more time to study the cases in the ward and to direct treatment in detail.

For these reasons it early became the rule in some of the general hospitals at the bases of the British Army in France to send all cases

[1] This paper appeared in full in Am. Jour. Med. Sc., November, 1919, No. 5, clviii, 629.

Service with the Harvard Unit, 22d General Hospital of the British Expeditionary Forces in 1916, 1917 and 1918, and attached to Casualty Clearing Stations at various times in 1917 and 1918.

of chest wound to specified wards, where they came under the care of a physician who was responsible for them whether operated on or not. This experiment having given satisfactory results, physicians later coöperated with surgeons at some of the casualty clearing stations situated in the forward areas, where most of the early operating was being done, and, in the spring of 1918, the second British army appointed a physician for each of their clearing stations to take charge of cases of chest wounds and placed the responsibility for directing this work upon the consulting physician of that army.

The mortality of penetrating chest wounds at the casualty clearing stations was seldom less than 20 per cent. There was a further mortality of about 5 per cent. in cases sent from the clearing stations to the base, and a number of cases, but what proportion I cannot say, died on the field, at the regimental aid posts or at the field ambulances. The total mortality for chest cases, including those complicated by other wounds, was probably not less than 30 per cent.

Therefore, the opportunity to save life by improved methods was clear, many individuals applied themselves to the problem so far as opportunity permitted and great advances in knowledge of the subject were made.

My experience with chest wounds extended over two years and was about equally divided between a general hospital near Boulogne and various casualty clearing stations, to which I was attached from time to time. I have notes, but not as complete as could be wished, of between 400 and 500 cases, probably less than half the number that passed through my hands.

It should be borne in mind that conditions of work vary much in different places, and at different times in the same place, and that methods had to be adapted to conditions as they existed at the time.

None of the hospitals in which I worked had special equipment or facilities for handling chest cases. They were in no way comparable to the few fortunate hospitals of Depage and others. Nevertheless, the average of efficiency in the British hospitals in France was extremely high. Their staffs of medical officers, nurses and nursing orderlies were ample for ordinary times, but whenever there was

heavy fighting on that part of the front, much that might have been desirable to do was perforce neglected and pressure for available beds required evacuation at the earliest possible moment of every case that would not die of the journey. Consequently, no cases could be held for study. At the clearing stations even the severely wounded were seldom retained for more than a week.

Chest Wounds at a Casualty Clearing Station. The first question in chest cases is whether an operation should be performed. In reaching a decision the main points to be considered are the nature of the external wounds and of the missile which caused them, the probable intrathoracic lesions, the condition of the patient and the time elapsed after wounding.

Other problems of interest center around the preoperative and postoperative management, the care of cases not operated on and the diagnosis of the lesions resulting directly or indirectly from the wound. It is these groups of problems rather than those related to operation which are the more likely to interest the physician.

The Preliminary Treatment. He who sees cases of chest wound when they arrive at the clearing station after a trip of eight miles or more in an ambulance, much of the way over rough roads, will be impressed by the exhausted condition of nearly all having severe, penetrating wounds. He cannot but appreciate their need of rest, quiet and warmth. Consequently, he will limit his first examination to absolute essentials. If the patient has much dyspnea it must be known whether air is being sucked into the chest through an open wound and whether there is extensive edema of the lungs, or a large hemothorax or hemopneumothorax requiring aspiration. External bleeding, if present, must be checked at this time.

The sucking wound should be temporarily closed at once, for these wounds produce severe disturbance of circulation and respiration, and closure of them generally affords marked and prompt relief. A stitch is better than strapping, because it holds more surely and permits of subsequent examination of the region of the wound without letting more air into the chest.

Bleeding can generally be controlled by a pad or pack of gauze tightly strapped in place, and the dressing, as a rule, can be removed a few hours later without causing recurrence of the bleeding. A

few cases require to be sent at once to the theater on account of persistent hemorrhage, but probably most of these cases die before reaching the clearing station.

Pulmonary edema generally clears up if the patient is put to bed with the chest slightly raised to facilitate breathing, the bed heated and a dose of morphin, $\frac{1}{6}$ gr., and atropin, $\frac{1}{120}$ gr., administered subcutaneously. Posture seems to me of great importance. The pillows should be arranged like a wedge, with its apex under the lumbar spine and the thick part of the wedge under the shoulders and head. To raise the head only does little good, and, on the other hand, to sit the patient nearly upright is to invite further collapse by handicapping the circulation to brain and medulla. If the patient can breathe as well lying flat with only one thin pillow under his head, he should not be propped up at all. Several times I have seen a patient turn gray and the pulse almost disappear after half an hour of sitting up, but improve again after he had been laid down. When nurses have been told to give bed-rests to chest cases they generally place them nearly vertical instead of at the lowest notch. Pillows are preferable because it is not easy to raise a patient very high with them. If the patient is pale and the pulse weak, neither head nor chest should be elevated if morphin will enable the patient to breathe comfortably lying flat. It is difficult to judge of the effect of morphin and atropin on pulmonary edema in cases newly arrived, because the benefit of rest and warmth is undoubtedly great, and morphin was given all cases that were not soon made comfortable without it.

Pain may be slight, but sometimes it is severe enough to embarrass respiration and to be an important factor in causing exhaustion. Most of the cases that I saw at the clearing station had received from $\frac{1}{4}$ to $\frac{1}{2}$ gr. of morphin at the field ambulance, and many were still under its influence when they came to us. Those whose discomfort or pain persisted after getting to bed and who could not be made comfortable by posture were given a second dose of $\frac{1}{6}$ gr. of morphin, which was generally ample. It is a mistake to use more than is necessary, because morphin tends to leave the patient more irritable than before and less able to bear ensuing inevitable discomfort. Chest cases, in my experience, too, are more irritable than any other

class of wounded and more difficult to make comfortable. When severe pain persists in spite of reasonable doses of morphin, it suggests a piece of shell lodged in the pleural cavity or friction between the ends of broken ribs. The treatment for either is early operation. In one such case a hernia of lung was found caught between the ends of a broken rib.

Collapsed patients were sent to the resuscitation ward, where they were warmed and the foot of the bed elevated, provided this could be done without inducing dyspnea. Nearly all of these, on account of the nature of their wounds, were urgently in need of operation to prevent or to control infection. Cases that did not soon begin to improve under the treatment above mentioned seldom became decent operative risks. Solutions of glucose and salts were often used by the continuous drip method per rectum, but it is difficult to know what effect it had, because many cases did well without it.

Transfusion of blood will make some cases operable that would otherwise become heavily infected before an adequate operation could be performed. I believe that cases in which large external loss of blood has occurred should be transfused before any severe operation is undertaken. It is not easy to select these cases because the only reliable evidence, as a rule, is the finding of large amounts of blood in the dressings of the patient on arrival; but if dressings were renewed and hemorrhage stopped at the field ambulance evidence of hemorrhage is lacking. On the other hand, collapse from shock or from exhaustion simulates conditions resulting from hemorrhage. When the presence of a large hemothorax suggests that loss of blood has been chiefly internal, transfusion seems to me contra-indicated for two reasons: (1) lest it add to existing circulatory embarrassment directly, and (2) lest it induce further internal hemorrhage. In abdominothoracic wounds with intraperitoneal hemorrhage transfusion is not likely to do good until after operation. It is dangerous, I think, whenever dyspnea is marked, whether associated with large hemothorax, pneumothorax, pulmonary edema or massive collapse of the lung.

Diagnosis. The difficulty of diagnosis in some serious cases will be apparent when it is realized that the patient needs rest, that examination fatigues him, that he must be roentgen-rayed before

operation, and that he should be in the theater and in condition to stand the operation with the least possible delay.

Moreover, he cannot take a deep breath, as his apex impulse is seldom palpable at this time; the anterior portions of the lungs are often hyperresonant; frequently there is subcutaneous emphysema of parts of the chest wall, causing a tympanitic percussion note; in other parts there are wounds; both lungs may be damaged; there may be pulmonary edema, bilateral hemothorax, massive collapse on the unwounded side, and on the wounded side simple hemothorax, pneumothorax, more or less collapse, hemorrhagic infiltration, more or less extensive, or any combination of these.

Displacement of the heart in the same direction may be caused by massive collapse on one side or hemothorax on the other, or by both together.

Moreover, wounds which do not penetrate the pleura frequently cause hemoptysis, not rarely hemothorax, and sometimes extensive collapse of the lung.

On the second day after wounding, and subsequently, patients can be examined more easily than on the first day. They breathe more naturally, and the signs, for some reason which I do not understand, seem to be more definite.

Fluoroscopic examinations were made in all cases having retained missiles, and in many others, as an aid to diagnosis of the intrathoracic condition. Sometimes a foreign body which had entered the chest would be found in the abdomen or liver, or the wound of entrance and the position of the foreign body in the chest might show that it must have injured the diaphragm. The roentgen-ray examinations were made in a standard position with the screen, the patient lying flat on his back on the stretcher with a half-blown air cushion under the head and shoulders. Displacement of the heart was looked for and the shadows were described. The radiologist could distinguish hemothorax, as a rule, without difficulty. With hemothorax of large or moderate size the heart was seen to be displaced toward the opposite side. The diaphragm was visible, as a rule, when the hemothorax was small and sometimes when it was of moderate size. The position of the diaphragm in these cases when seen was regularly reported by Capt. Finzi, R.A.M.C., as

being elevated and its movement restricted on the side of the hemothorax. Another radiologist frequently reported the diaphragm depressed and flattened with hemothorax, but I think that the raised position was the more usual. Hemorrhage into the lung along the track of the missile often gave a shadow distinctly visible. Shadows in the opposite lung not due to direct injury were sometimes attributed to more or less extensive collapse of the lung. The condition was spoken of as "contralateral collapse." The shadows were wedge-shaped, the base toward the lateral chest wall and the apex toward the spine. Generally, there was an area of better illumination at the extreme base and in the costodiaphragmatic angle which served to differentiate the condition from hemothorax.

Preliminary Aspiration. In a small proportion of cases in which a large hemothorax or hemopneumothorax exists it may cause a positive intrathoracic pressure on the affected side, with the result that dyspnea renders the patient's condition unsatisfactory for operation. Moreover, opening the chest would lead to a sudden reduction of this pressure, and in cases in which the mediastinal contents are freely movable might result in added disturbances of circulation or respiration. Therefore, in such cases, it has seemed to me best to aspirate as a preliminary to operation, and to endeavor to leave the intrathoracic pressure at approximately that of the atmosphere, or, in other words, to withdraw only as much as can be easily obtained without suction. To empty the chest so soon after wounding would be to run the risk of recurrent hemorrhage.

By a series of observations of intrathoracic pressure in hemothorax[1] measured in centimeters of water, it was found that intrathoracic pressure might sometimes be reduced by as much as 12 cm. by the removal of not more than 780 c.c. of fluid. The negative pressure so produced would be suddenly neutralized the moment the chest was opened at operation. This last disadvantage, however, can be overcome in large measure by the use of gas-oxygen anesthesia and a positive pressure of the anesthetic while the chest is open. Major Geoffrey Marshall, R.A.M.C., when in charge of anesthetics for the Second British Army in 1918, used positive anesthetic pressure for thoracotomy operations with marked success.

[1] Shattuck and Welles: Quarterly Jour. Med., April, 1919.

Post-operative Management. *Post-operative Aspiration.* When, by a radical operation, the hemothorax has been evacuated, bone fragments and foreign body removed and the chest closed, fluid soon begins to collect in the pleural cavity. Its rate of increase is probably determined chiefly by the amount of residual infection. To limit this accumulation and to promote reëxpansion of the lung it became the practice to aspirate once at least after operation. The rule which I followed was to aspirate after twenty-four hours had elapsed and again two days later. In the most favorable cases 200 or 300 c.c. of fluid and some air were obtained at the first tap, and so little fluid at the second that further tapping was superfluous. In all instances a specimen of fluid was sent to the laboratory for aërobic and anaërobic cultivation, so that infection, when present, should be quickly recognized.

Lockwood and Nixon[1] reported excellent results in a number of infected chests which had been cleaned out as far as possible by operation, closed and aspirated. In spite of infection demonstrated after operation they aspirated repeatedly instead of resorting to secondary drainage. I have no doubt that their example could be followed to advantage in certain types of cases, but believe that if aspiration is to be relied on to keep an infected chest clear of fluid it is essential to have the use of a portable roentgen-ray apparatus which can be used in the ward. By this means, and by no other, I think, can there be any assurance that all the fluid has been in fact removed. Lockwood and Nixon used such an apparatus and considered it indispensable.

For two days after severe operations morphin was used freely to relieve pain and to check the restlessness of discomfort. Cases doing well did not require its longer continuance.

Pulmonary Edema. Some patients who had been operated on and others who had not were troubled by attacks of dyspnea and wheezing or rattling in the chest associated with light frothy expectoration. The attacks came on sometimes late at night, in other cases in the evening and in still other instances the symptoms began in the daytime.

The mildest attacks were those that came on late at night. The

[1] British Med. Jour., January 26, 1918, p. 105.

condition in these cases was quickly relieved by a dose of morphin $\frac{1}{6}$ gr., and atropin, $\frac{1}{120}$ to $\frac{1}{100}$ gr., subcutaneously. When the attack began in the evening relief was temporary, and a second dose was required in the course of the night. When frothy expectoration first appeared in the daytime it yielded less readily to drugs, and the edema usually became more marked during the night.

The frothy expectoration occurred in two groups of cases, namely —in the later stages of cases that were more or less infected and in the early stages of severely wounded cases, especially when exhausted by travel. In the later stages the froth was white, but sometimes it was mixed with the purulent sputum of bronchitis. The response to drugs was best when there was no bronchitis sputum and correspondingly less when it predominated. Pulmonary edema coming on in the daytime was a bad prognostic sign.

Among the group of cases in which pulmonary edema appeared early there were some which arrived at the clearing station in this condition. As might be expected so soon after wounding the froth was tinged with blood and was often mixed with thick mucus or blood. In these cases also the result of medication seemed to depend a great deal on whether or not the sputum consisted chiefly of froth or mainly of viscid material and blood.

Cases not Requiring Early Operation. These cases consist of two groups, namely—those whose condition is apparently hopeless and those which may be expected to do well without operation.

Some of these last require aspiration for relief of symptoms or to hasten convalescence, and others develop intrathoracic infection, calling for operative interference later. Their special problems are discussed in the paragraphs which follow.

Intrathoracic infection in chest wounds commonly follows penetration of the chest by a large shell fragment. It seldom results from a bullet or shrapnel ball except in the comparatively small number of these cases having extensive bone damage. Early operation is indicated in the cases likely otherwise to become infected. The remainder should not be operated on unless evidence of infection appears later. The important thing is to watch for signs of developing infection and to recognize it promptly if it appears. Nearly all cases of penetrating wounds have enough hemothorax to make it possible to withdraw a sample to be cultured in the laboratory.

This should be done for all cases of hemothorax that are to remain in the hospital long enough to get a report.

Fever of a moderate degree is the rule in sterile hemothorax, but after a few days it begins to subside. Case I is an example, but in this case the fever lasted considerably longer than is common in the absence of infection. The two negative reports on the chest fluid and the final subsidence of the fever indicate that if infection was present at all it was inconsiderable. Infection generally begins to give signs on or after the third day, although cultures of chest fluid will often show its existence earlier.

Infection should be suspected when the temperature and pulse do not show a downward tendency after a few days, when the amount of fluid in the chest seems to be increasing, when the patient's condition does not rapidly improve, or when after temporary improvement he becomes abnormally irritable, complains of intrathoracic pain and the temperature begins to rise again.

An early sign of infection to which Capt. Adrian Stokes, of the Royal Army Medical Corps, called my attention is well-marked hemolysis in chest fluids obtained within three days of the wounding. Hemolysis developing later is so common in chest fluids which remain sterile that it has no considerable diagnostic value after the first three days.

Infection with streptococcus causes a rapid increase of fluid in the chest. The infection may develop early or late, and when it comes early may be combined with infection by other organisms. The streptococci found in the chest were of two principal types, hemolytic and non-hemolytic. Both organisms generally caused serious infection, but the hemolytic type seemed to be particularly virulent. The mortality of infected hemothorax following early resection of a rib and open drainage is very high, so much so that anything which offers hope of reducing it should be tried. The mortality is lower when the infection does not appear until the end of the first week or later. Open drainage after the first week disturbs the respiration and circulation far less than is the case when it is performed earlier. This can be explained on the supposition that adhesions have formed and the cavity become walled off by a thick layer of fibrin. Certain it is that in these cases of late opera-

tion very little air passes back and forth through the drainage tube, whereas in cases of early drainage the reverse is true and the patient can only be made comfortable by preventing the inrush of air during inspiration by applying some kind of valve as a part of the dressing.

Aspiration of Infected Chests. In the summer of 1918 I treated eight or nine cases of early infected hemothorax by daily aspiration for a week before resection was performed. It was hoped in this way to limit the infection to a smaller cavity and to reduce mortality. After each aspiration the patients generally felt more comfortable, and in several cases the pulse and the temperature dropped in the course of a few days to nearly normal, only to rise again later. The attempt to reduce the size of the cavity to be drained was not apparently successful. In some cases the reduction of toxemia was slight and transient, in others marked benefit resulted, but was followed after a few days by recurrence of toxemia. In all cases emaciation developed rapidly. The failure to get all the results hoped for can be attributed to the difficulty of draining completely by aspiration a collection of fluid containing large and increasing amounts of coagulum and having a marked tendency to collect in pockets.

No case of hemolytic streptococcus infection was included in this series. One case had gas-bacillus infection. His condition on admission was such that operation was not then considered. Following aspiration of the chest, little if any walling off took place. Two small transfusions gave temporary benefit and resection was finally performed, but the patient died after about two weeks.

The other cases had non-hemolytic streptococcus. It seemed to me that the marked temporary improvement shown by some of them indicates that aspiration within the first five days followed by open drainage is probably less dangerous than open drainage performed earlier. Operative drainage, I think, should not be delayed as much as a week, but should be performed the moment improvement after aspiration ceases. Control observations by means of a portable roentgen-ray apparatus would have been valuable.

Pneumococcus infections of the pleural cavity tend to die off quickly and some of them can be cured by aspiration alone. The same is true of some cases of staphylococcus infection. Cases of

gas-bacillus infection may show very marked symptomatic improvement after aspiration. Unless there is concomitant infection with other organisms it is probably good practice to aspirate them once at least before operation. This should certainly be done if accumulation of gas or a large amount of fluid embarrasses respiration or circulation. The gas bacillus is by no means as virulent in the pleural cavity as it is in the muscles.

Aspiration cannot be relied on for more than temporary relief for cases having large retained fragments of shell plus the cloth and bone fragments usually carried in by them. Early radical operation offers the only hope for these cases. Aspiration as a cure for infection should be tried only when the infection develops late, is of a mild type or follows a radical cleansing operation.

A portable roentgen-ray apparatus would add materially to the safety and advantage of this method, because plates could then be taken without fatiguing the patient and it would be possible to determine after aspiration whether all the fluid had been removed.

Hemothorax. For purposes of description, hemothoraces can be divided into three classes: the small, in which the pleural cavity contains not more than 500 c.c. of bloody fluid; the moderate, containing from 500 to 1000 c.c.; and the large, hemothoraces of from 1000 c.c. upward.

The physical signs of a small hemothorax are dulness below the angle of the scapula, with all other signs diminished and more or less aëgophony. The aëgophony is not pronounced, but, I think, it is the most valuable single sign of fluid in these cases.

So far as I have been able to ascertain from the somewhat conflicting reports of various radiologists the diaphragm is usually high and moves little from the first days after wounding. It was early learned that exploratory tapping to demonstrate the pressure of small hemothoraces was generally successful even when signs were very slight, provided the puncture was made midway between the spine and the posterior axillary line in the interspace lying under the angle of the scapula. To uncover this interspace the hand of the patient was carried to the shoulder of the opposite side. Exploratory taps made lower down frequently failed to show the presence of fluid. In other words, the fluid in a small hemothorax lies higher

than is the case with pleural effusion or the common form of empyema secondary to pneumonia. In the early days of hemothorax it seems improbable that settling out of fibrin or the formation of adhesions in a sterile hemothorax could account for failure to obtain fluid lower down.

These observations strengthen the view that the diaphragm in small hemothoraces is generally at a high level.

The apex impulse of the heart is not notably displaced, but the roentgen rays may show slight displacement away from the fluid, indicating a reduction of negative pressure in the affected side of the chest.

The hemothorax of moderate size gives physical signs like the small one, but more marked. Cardiac displacement cannot often be demonstrated in the first few days after wounding without putting the patient through a more rigorous examination than seemed ordinarily justifiable or necessary. The apex impulse is often impalpable at this stage. Symptoms in these cases do not render aspiration urgent.

When I began to examine cases of hemothorax I assumed that the changes in the breath sounds over the retracted lung near the upper limit of the fluid would be the same as in the ordinary case of pleural effusion. I expected the breath sounds to be diminished in intensity but typically bronchial in character. It was found, in most cases, however, that their quality was not typically bronchial, but rather more amphoric. They might perhaps have been described as bronchoamphoric, partaking, as they did, of both qualities. Sometimes they were almost purely amphoric as in typical pneumothorax. Nevertheless, exploratory tapping over the point of greatest intensity of this breathing yielded over and over again fluid only. Neither was air often obtained, as below stated, by aspiration. (See Pneumothorax.)

The intensity of the breath sounds over a hemothorax is almost invariably diminished above and still more diminished or absent below.

Retraction or flattening of the chest-wall below the clavicle in front, or below the angle of the scapula behind, or at both points, was observed in a great many cases of hemothorax examined at the

Twenty-second General Hospital. This phenomenon seemed to be less frequent and less marked the first few days after wounding than after a week or more from the date of injury.

This condition associated, as it appeared to be, with a high diaphragm, points in these cases to collapse of the lung over and above that induced by the mere presence of fluid. (See Massive Collapse below.)

That the diaphragm may be depressed, and probably is depressed, as a rule, by large collections of fluid or of fluid and air in the pleural cavity, seems altogether likely. In such cases, however, the shadow of the hemothorax is so dense that the radiologist cannot locate the diaphragm with certainty.

Aspiration for Hemothorax. Hemothoraces of about 2000 c.c., associated with dyspnea and rapid pulse, were aspirated as soon as possible, with the object of relieving distress, but no attempt was ordinarily made to empty the pleural cavity within the first week after wounding lest recurrence of intrapleural hemorrhage be induced by the production of a high negative intrathoracic pressure. A large hemothorax suggests damage to a large vessel and relatively greater danger of recurrent hemorrhage into the pleural cavity.

To aspirate a small sterile hemothorax seems scarcely worth while, and it has seemed to me wiser to do nothing than to aspirate except to relieve symptoms in the first few days after wounding. To disturb intrathoracic conditions at this time is to violate the principle of rest to the injured part, and perhaps to increase the chance of intrapleural infection.

For hemothoraces of moderate size, in which fever persisted, it was my practice not to aspirate before the end of the first week, by which time the distress consequent upon recent injury to the chest had passed. Fever develops even with sterile hemothoraces. The temperature generally dropped to near normal on the day following aspiration, and the patient often said he could breathe more freely. The purpose was to shorten convalescence by leaving less to be absorbed from the pleural cavity and by reducing fever.

Exploratory tapping was frequently performed as an aid to diagnosis or to obtain a specimen of fluid for aërobic and anaërobic cultivation. This should be done as soon as possible, and by routine, in order to detect infection at an early stage. A negative

result does not rule out infection, which may be missed because local, but may later become general in the pleural cavity.

Replacement of fluid by oxygen is advisable if more than 700 c.c. of fluid is to be withdrawn. The removal of larger amounts of fluid causes a marked change of intrathoracic pressure, generally causes cough and pain which interrupt the work, and may, perhaps, favor infection of the pleural cavity or bring on intrapleural hemorrhage.

Oxygen Replacement.—By means of oxygen replacement a very large hemothorax may be evacuated without pain or discomfort. It is good practice, I think, to withdraw 500 c.c. of fluid before beginning to replace, and after that to replace fluid withdrawn with an equal amount of oxygen, allowing it to run in simultaneously. This method is quicker, easier and more comfortable to the patient than alternately to withdraw fluid and put in oxygen (Shattuck and Welles, see footnote on p. 73.)

Difficulty occurs when there are small clots in the fluid which repeatedly plug the aspirating needle or when there is massive clotting of the blood. In other cases the method of Palfrey works expremely well.

Hemopneumothorax. If cases of hemopneumothorax were numerous I generally failed to recognize them by physical examination, aspiration or by roentgen rays. I cannot but believe, however, that many more cases existed than were recognized. That small amounts of air should not have been found by roentgen rays is not surprising, because most of the screening was done with the patient lying on his back. To have done otherwise would have exposed the patients to unnecessary distress and fatigue, and the greater amount of time required for such an examination would have seriously interfered with other urgent demands on the radiologist.

Large hemothoraces requiring early aspiration for relief of symptoms not infrequently yielded considerable amounts of air as well as fluid. In less urgent cases aspiration was postponed for a week or more and small quantities of air, if originally present, might have been absorbed in the meantime. Whatever the reason, air was seldom obtained when aspirating small or medium-sized hemothoraces.

It has been believed by some that a small amount of air associated

with a hemothorax will cause much greater cardiac displacement than would result from a similar volume of fluid alone. I hesitate to believe this failing a rational explanation for a phenomenon which would seem to contravene physical laws. If pressure in the air were greater than that in the fluid, would not the fluid float on the air? If air-pressure is not greater than fluid-pressure, why should it displace the heart more?

Massive Collapse of the Lung. The occurrence in cases of chest-wounds of collapse of considerable portions of lung tissue for no known cause is a most interesting fact.

This subject has been so well handled by Sir John Rose Bradford,[1] who was one of the British medical consultants in France, that I shall not discuss it in detail. The collapse may occur in the wounded lung, in the uninjured lung or in both lungs. Apparently, it most often affects only a part of one lobe, but in some cases it is very extensive, and it then causes very marked cardiac displacement by drawing the heart away from the opposite side of the chest.

If, for example, a bullet has passed through the left side of the chest without causing much damage, but leaving behind a small hemothorax, one expects to find no marked cardiac displacement and no abnormal signs in the right chest unless extensive collapse has occurred in the right lung, when the cardiac impulse will be found near the right nipple; the right side of the chest will be immobile and retracted; there will be extensive dulness; the breath sounds may be bronchial or absent; and the roentgen-rays will show a shadow over the right side of the chest, a high, immobile diaphragm, and the dorsal portions of the ribs will form a more acute angle with the spine on the right than on the left.

Cases of such extensive collapse are easy to recognize, but they are rare. Lesser degrees of collapse are probably common but difficult to diagnose with certainty. The possible presence of more or less collapse in either lung in any case of chest wound renders interpretation of physical signs difficult and uncertain. A common error is to mistake the collapse for pneumonia or for fluid. The position of the apex impulse is the key.

[1] Quarterly Jour. Med., xii, 127.

Chest Wounds at the Base. The problems at the base hospital differ from those at the clearing station mainly from the fact that patients arrive later, that most of the bad cases have been eliminated by death or improved by operation, and that, as a rule, the patients arrive too late for radical operation, designed to prevent infection.

What is most needed is to combat existing infections of the parietes or intrathoracic structures, and to keep a sharp lookout for complications, and for infections which may develop late.

Pulmonary edema is sometimes induced by the journey and develops at night in some infected cases. The treatment has been described above.

Massive collapse is seen at the base hospital as well as in the zone of the armies.

The questions relating to sterile hemothorax can be most advantageously studied at the base hospital.

Summary. Under the war conditions met with a physician could render valuable service either at an advanced operating center or at a hospital in the rear by coöperating with the surgeon who did the chest operations, or even by becoming responsible for the treatment of all cases of chest-wound, whether operated on or not. The selection of cases for operation, their preliminary treatment and after-care were left mainly in the hands of the physician after he had learned to select the types of cases which operation could be expected to help.

When urgency of work does not require the constant presence of the surgeon in the operating room, however, he will do well to take personal charge of the post-operative cases himself, and should confer with the physician whenever doubt arises as to the best course of treatment to pursue either before or after operation.

There are many points of technic still to be worked out regarding the best methods of operating and the care of post-operative chest cases, which the surgeon can never appreciate unless he himself follows closely the cases he has operated on.

Close coöperation between one physician and one surgeon is essential to the best results and a strong nursing staff is absolutely necessary if treatment is to be satisfactorily carried out.

The management of cases not requiring operation, the diagnosis

of intrathoracic lesions and the treatment of some of the most serious symptoms is essentially medical work.

Aspiration may be useful (*a*) as a preliminary to operation or to relieve symptoms when a large hemothorax or hemopneumothorax exists; (*b*) it should be performed after thoracotomy and closure of the chest; (*c*) infected hemothoraces should, in some cases, be aspirated for several days before open drainage is resorted to. A few will recover by aspiration alone.

Sterile hemothoraces, probably, should not be aspirated, unless causing symptoms, until a week or more after wounding, lest infection be drawn into the pleural cavity.

Replacement with oxygen is useful in cases of certain types.

It is a pleasure to thank Surgeon-General Sir John Rose Bradford and Colonel A. B. Soltau, of the British Medical Service, for helpful advice and information.

FACTORS INFLUENCING RECOVERY AND RESOLUTION IN LOBAR PNEUMONIA:

WITH SPECIAL REFERENCE TO THE CHEMISTRY OF THE PNEUMONIC EXUDATE

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Various factors may be operative in the recovery from lobar pneumonia and in the resolution of the fibrinous exudate:

1. Previous Observations with a Bearing on Recovery and Resolution. Recovery from lobar pneumonia is at present thought to be due to the elaboration of protective substances during the course of the disease. Through the work of G. and F. Klemperer,[1] Neufeld and Haendel,[2] Dochez[3] and Clough[4] the blood serum from patients at about the time of or after the crisis has been shown by animal experiments to possess protective power against otherwise fatal doses of pneumococci. These protective substances in small amounts are usually present, but at times are not demonstrable at all. The use of both pneumococci and serum from the same patient is important in their recognition.

An advance in the study of the mechanism of recovery is the demonstration by Bull[5] of the importance of agglutinins in the disappearance of pneumococci from the blood, and by Cole[6] of soluble inhibiting substances in the blood with the property of neutralizing pneumococcus antibodies.

[1] Berl. klin. Wchnschr., 1891, xxviii, 833, 869.
[2] Ztschr. f. Immunitätsforsch., 1909, iii, 168; Arb. a. d. k. Gsndhtsamte., 1910, xxxiv, 166.
[3] Jour. Exper. Med., 1912, xvi, 665.
[4] Bull. Johns Hopkins Hosp., 1913, xxiv, 295.
[5] Jour. Exper. Med., 1915, xxii, 457.
[6] Ibid., October, 1917, xxvi, 453.

It is, of course, possible that the methods at present available for the demonstration of humoral immunity are inadequate and that it is a more potent factor than animal tests indicate. The inconstant presence and small amount of the protective substances, however, suggest that the humoral factors, while important, are, by themselves alone, an insufficient explanation of so striking an incident as the crisis in pneumonia.

In explanation of resolution, it has long been clear that enzymatic action must account for the solution of the exudate. Sörensen[7] called attention to the important relation between H-ion concentration and enzymatic processes in general. Dernby's[8] work on the autolysis of animal tissue has been of assistance in suggesting methods applicable to the investigation of enzymatic processes in the pneumonic exudate.

II. Other Factors Influencing Recovery. The following data suggest that local biochemical changes as well as humoral factors may be of importance in recovery from pneumonia. These may be grouped under these headings:

1. *Acidosis in Pneumonia.* Various observations have shown that in the metabolism in pneumonia a considerable amount of acid is produced. This is indicated by a diminished carbon dioxid content of the blood, an increased ammonia output in the urine, an increased titrable acidity, and an increased alkali tolerance. In his study of 30 cases of pneumonia, Palmer[9] found that in many, usually the more severe cases, the urine contained a large amount of an organic acid which is free at a H-ion concentration of 5.0.

2. *Partial Isolation of the Pneumonic Lung.* The exudate fills the alveolar spaces and is separated from the general circulation by the limiting alveolar wall. Kline and Winternitz[10] have shown that the pneumonic lung in experimental pneumonia communicates imperfectly with the circulation. This partial isolation suggests that within the involved region biochemical changes may occur which are reflected only to a limited degree in the body as a whole.

[7] Enzymstudien über die Messung und die Bedeutung der Wasserstoffionenkonzentration bei enzymatischen Prozessen, Biochem. Ztschr., 1909, xxi, 131.

[8] Jour. Biol. Chem., August, 1918, xxxv, 179.

[9] Jour. Exper. Med., October, 1917, xxvi, 495.

[10] Ibid., 1915, xxi, 311.

An increase in H-ion concentration of the exudate may thus occur without a change in H-ion concentration of the blood.

3. *Acid Death Point of the Pneumococcus.* Experiments with the pneumococcus[11] indicate that it is susceptible to varying H-ion concentrations. The production of acid is the most important bactericidal factor in the short viability of the pneumococcus in glucose bouillon cultures. Such cultures, allowed to grow and die out, usually reach a final H-ion concentration of about 5.1. The exposure of living pneumococci to 5.1 or a higher H-ion concentration shows that the organism does not survive longer than a few hours in a H-ion concentration of about 5.1, and that it may live for at least many days at 7.4 to 6.8. In the intervening H-ion concentrations, between 6.8 and 5.1, the pneumococcus is killed with a rapidity which bears a direct relation to the H-ion concentration, that is, the greater the acidity, the more rapid the death. The following observations suggest that some other factor, also influenced by the degree of acidity, may be responsible for destruction of pneumococci:

4. *Dissolution of Pneumococci.* As shown by Lord and Nye,[11] a critical degree of H-ion concentration has a bearing on dissolution of pneumococci. Cloudy suspensions of washed pneumococci in H-ion concentrations varying from 8.0 to 4.0 show, after incubation, disappearance of organisms apparently due to their dissolution in lower H-ion concentrations than about 5.0. This dissolution is most marked at about 5.0 to 6.0; some also takes place toward the more alkaline end of the scale. An enzyme set free from the bacteria themselves may be the explanation. Dissolution of pneumococci under the favoring influence of a change in H-ion concentration may be a factor in the disintegration of organisms observed in the pneumonic exudate in the more advanced stages.

5. *H-ion Concentration of the Pneumonic Lung.*[12] The H-ion concentration of the press juice from the pneumonic lung at necropsy in fatal cases is higher than that of other tissues of the body, and

[11] Lord, F. T.: Tr. Am. Soc. for Clin. Investigation, 1916, p. 8; Bronchopulmonary Disease, Jour. Am. Med. Assn., December 30, 1916, lxvii, 1981; Relation of Pneumococcus to Production of Acid in Fluid Culture Mediums and Reaction of Pneumonic Lung, ibid., 1919, lxxii, 1364. Lord, F. T., and Nye, R. N.: Jour. Exper. Med., October, 1919, xxx, 389.

[12] Lord (footnote 11).

reaches a p_H of about 6.0. The pneumonic exudate in experimental Friedländer and pneumococcus pneumonia in dogs may likewise be more acid than the press juice of other organs and the blood. In one dog with experimentsl pneumococcus pneumonia killed on the third day, the H-ion concentration of one involved lobe, taken immediately from the body, was 6.0, and that of another 5.4. From the former, pneumococci were grown in pure culture, but from the latter no growth of pneumococci was obtained.

The pneumococcus can usually be cultivated from the pneumonic lung after death, even when the H-ion concentration is about 6.0. To judge from the observations on the acid death point of the pneumococcus, however, slightly higher H-ion concentrations than this, as in the dog's lung with a p_H of 5.4, would probably have resulted in death of the organisms.

These observations were made, using the colorimetric method after dialysis through a celloidin membrane. It is desirable that the H-ion concentration of the pneumonic lung and its influence on the pneumococcus in the tissue itself be determined during the course of pneumonia in the living subject by the electrometric method.

III. Factors Influencing Resolution. As has been shown elsewhere,[13] cellular material obtained from the pneumonic lung in the stage of gray or red-gray hepatization contains a proteolytic enzyme capable of digesting coagulated blood serum at an H-ion concentration of 7.3 to 6.7 inclusive and inactive in more acid concentrations. Such cellular material also contains a proteolytic, peptone-splitting enzyme operative at H-ion concentrations of 8.0 to 4.8 inclusive and most active at 6 3 or 5.2. A digestive action on coagulated blood serum probably indicates a similar action on fibrin, the split product of which is then acted on by a second enzyme and reduced to amino-acid. The products of protein digestion may thus be converted into a form in which they can be absorbed.

The finding of two enzymes in the pneumonic exudate, one digesting coagulated blood serum in weakly alkaline and weakly acid

[13] Lord, F. T.: The Relation of Proteolytic Enzymes in the Pneumonic Lung to H-ion Concentration, an Explanation of Resolution, J. Exper. Med., October, 1919, xxx, p. 379.

mediums and the other splitting peptone to amino-acid nitrogen with an optimum activity in still more acid mediums, may serve to suggest, independently of the previous observations, that the pneumonic exudate undergoes an increase in H-ion concentration, according to the principle Michaelis[14] established for enzymes in general, that the H-ion concentration of tissue fluid, containing specific enzymes, is the same as that at which the enzymes work best.

IV. Local Biochemical Changes as an Explanation of Recovery and Resolution. The findings suggest a theory in explanation of recovery from pneumonia in the course of which humoral immunity is assisted by local biochemical changes. Acidosis in pneumonia may be due to partial isolation of the pneumonic lung, permitting a local increase in H-ion concentration, the excess of acid formed in the exudate gaining entrance to the circulation. Dissolution of the pneumococcus may proceed at first slowly and later more rapidly as the local acidity increases. When the local H-ion concentration reaches the acid death point of the pneumococcus, crisis and recovery follow.

The findings also suggest an explanation of resolution in the course of which the fibrinous exudate is locally split to a form in which it may be readily and harmlessly absorbed. With the breaking down of the cellular exudate, an enzyme digesting protein (fibrin) in weakly alkaline and weakly acid mediums is liberated. As the acidity increases, the action of this enzyme ceases. An enzyme capable of splitting peptone to amino-acid nitrogen, also active during the proteolysis of the fibrin, is still further activated at an H-ion concentration of 6.3 or 5.2. The exudate may thus be dissolved, and resolution takes place.

DISCUSSION

Dr. Emanuel Libman said that the question of acid production by bacteria was of the greatest interest in connection with the development of disease processes.

In 1901, in a paper dealing with the peculiarities of bacterial activity on media containing carbohydrate, he had pointed out the great importance

[14] Michaelis: Die Wasserstoffionenkonzentration, Berlin, 1914, p. 86.

of acid production in the body by bacteria. At that time he found that while pneumococci produced considerable degrees of acidity on such media, precipitation of the proteid did not occur unless there was over 1 per cent. of the carbohydrate present. Streptococci, on the other hand, possessed this faculty even in the presence of 0.1 per cent. of glucose.

In the body, conditions must be quite different. It had been shown by Rosenow, and later by Longcope, that if one grew pneumococci in normal human serum very little acid was produced, but if grown on serum of patients suffering from pneumonia, very marked acid production and coagulation developed.

It was believed that the pneumococci had developed the power of producing acid from glycoproteids. In a patient suffering from pneumonia there would, on theoretical grounds, be present very marked acid production, with precipitation of proteid.

Dr. S. Solis Cohen remarked: Does Dr. Lord attribute the high acidity to autolysis or to some direct biochemic activity of the pneumococcus or its enzymes? I could not make out his view. This splendid study, which adds so much to our knowledge, is along a line of great importance. The crisis is the key to both the pathological and the therapeutic problem in lobar pneumonia, and the exudate is of importance both in disease and in recovery. Certain studies made at my suggestion by Drs. Kolmer and Weiss have shown the presence in the exudate of something—which, however, we have not been able to identify or isolate—that possesses distinct toxic properties, we have called it "pneumonic lung-extract" to indicate its origin and avoid premature theory of its nature. "Pneumonic lung-extract" is quickly fatal to rabbits, guinea-pigs and mice, and hemolyzes human red cells *in vitro*. We cannot obtain a similar extract from the healthy lung.

Dr. Lord stated that, in answer to Dr. Hoover's question, the H-ion concentration of the pneumonic lungs was determined by the colorimetric method after dialysis of the press juice obtained from the lungs. In one case the colorimetric determination was checked by the electrometric method. In answer to Dr. Cohen, I can only speculate as to the source of the acid which led to an increase in the H-ion concentration of the pneumonic lung. Perhaps the most likely source is the splitting of the small amount of sugar in the blood. There are, however, other possible sources. Whether the increased acidity is due to autolysis, biochemic activity of the pneumococcus or some other cause I do not know.

OBSERVATIONS ON THE PRODUCTION OF AN ANTI-HEMOTOXIN FOR THE HEMOTOXIN OF BACTERIUM WELCHII (BACILLUS AËROGENES CAPSULATUS)

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It has previously been shown by Ford and Lawrence[1] that the hemolytic property of milk cultures of Bacterium welchii is to be attributed to the production of a true bacterial hemolysin or hemotoxin by this organism. The opinion previously held that the destruction of blood corpuscles in cultures of this species is due to the presence of acids (butyric and lactic) is not justified since milk cultures retain their blood-laking powers after complete neutralization. In tests with the neutralized whey the discoloration of the corpuscles due to the production of methemoglobin from acids is not seen and the hemolized blood takes on the brilliant red color usual with true bacterial hemotoxins. Furthermore, cultures of the gas bacillus lose their hemolytic activity on heating to 62° to 63° C., while solutions of both butyric and lactic acids can be boiled some time without losing their power to destroy blood corpuscles. Finally the hemolysin of Bacterium welchii is digested by pepsin-HCl and by pancreatin, and is precipitable by ethyl alcohol, properties which also tend to place this substance in the group of bacterial secretory products. During the course of the past few months the study of

[1] Hemolytic Substances in Heated Milk and in Milk Cultures of Bacterium welchii, Johns Hopkins Hospital Bulletin, August, 1917, No. 318, xxviii, 245.

the hemotoxin of the gas bacillus has been continued and our previous observations have been confirmed. In addition several new facts have been brought out which it seems desirable to report at the present time.

Source of the Cultures. The strains of Bacterium welchii which have been employed for the study of the hemolysins found in milk cultures have been obtained in all instances from samples of Baltimore milk. Quantities varying from 500 to 1000 c.c. have been heated to temperatures ranging from 80° to 85° C. for twenty- to thirty minutes and incubated at 37° C. for twenty-four to forty-eight hours. In the majority of such samples the characteristic reaction of stormy fermentation appears after the lapse of this time. Such milk cultures contain aërobic bacteria and a number of other anaërobes in addition to the gas bacillus. Various methods of obtaining pure culture have been tried out. In the early part of the work rabbits were inoculated intravenously with small quantities (1 or 2 c.c.), killed in five minutes, kept in a warm place for eighteen to twenty hours and milk and agar cultures made from the blood and organs. Frequently other organisms survived in the animal body and appeared in the cultures, so that it was necessary to resort to the use of blood-agar plates from which the typical hemolytic colonies could be fished. As the work progressed it was found that this plating in agar could be dispensed with and pure cultures obtained from the animals by the simple method of "continuous transfer" of fairly large quantities of culture (1 to 2 c.c.) from one milk tube to another. The rapidity with which Bacterium welchii develops in milk at 37° C. enables it to overgrow nearly all other species, and if transfers be made at the end of every twelve hours some half-dozen transfers suffice to give an uncontaminated strain. Cultures obtained by this apparently crude method have been tested repeatedly. They contain nothing but non-motile encapsulated organisms, Gram-positive with an admixture of Gram-negative forms, give characteristic reactions in culture media and produce the typical lesions on animal inoculation. Blood-agar plates made from such cultures reveal nothing but hemolytic colonies and aërobic cultures remain sterile. We feel confident, therefore, that pure cultures can be obtained easily by this method. The

same method of continuous transfer can be applied to the original milk flasks which have shown the stormy fermentation and in about two-thirds of the samples a pure culture of the gas bacillus can be obtained. In a certain number, however, the gas bacillus is overgrown by certain acid-resistant streptococci, which may happen to survive the original heating of the milk. Animal passage, therefore, is usually advisable. It may be noted that the gas bacillus develops in milk tubes without incubation under anaërobic conditions, provided cream is left in the milk to form a surface layer. While this cream layer may be more pervious to oxygen than was previously supposed, and not provide anaërobic conditions in the depths of the medium, its presence in the milk has proved a distinctly favorable factor for the cultivation of the gas bacillus. Finally the difficulty of keeping milk cultures alive may be lessened by the addition of a few particles of powdered calcium carbonate to the milk tubes. The acidity of the cultures is much lessened by this procedure and transfers can be obtained from tubes twelve to fourteen days old. In general the gas bacillus dies out in milk in three or four days.

Preparation of the Hemotoxin. The hemotoxin of Bacterium welchii can be obtained from massive milk cultures of the organism by the following method: Large flasks of sterile milk, containing 800 to 1000 c.c., are inoculated by pouring into them the contents of a twenty-four to forty-eight hour milk culture (10 to 12 c.c.). These flasks are incubated at 37° C., and by the end of twenty-four to forty-eight hours the characteristic reaction usually appears. This material is now filtered through coarse filter paper to remove the particles of curd, and the filtrate as it appears is immediately neutralized by caustic soda or caustic potash. The filtration is usually slow, requiring eighteen to twenty hours, during which time there is a further development of organisms in the filtrate, with some increase of acidity. The material is again completely neutralized, upon which a thick gelatinous precipitate appears. This settles to the bottom of the flasks and is easily removed by passing through filter paper. If this product is not entirely free from bacteria it can now be filtered through a Berkefeld candle. The final solution is clear, straw-colored, somewhat viscid and foams easily on shaking. About 400 c.c. of this product can be obtained from a liter culture of the gas bacillus.

Strength of the Hemotoxin. Hemolytic solutions prepared by the method here described have a fairly uniform strength. When titrated against rabbits' corpuscles 1 c.c. of a 5 per cent. suspension of blood cells is usually dissolved completely by 0.05 c.c., representing a dilution of 1 to 20 of the original material. The reaction takes place somewhat slowly, requiring at least four hours at 37° C. In some instances the hemolysin is stronger than this, the hemolytic unit being 0.025 c.c., a dilution of 1 to 40, but this is somewhat uncommon. Very rarely a more powerful hemotoxin is found with a hemolytic unit of 0.01 c.c., a dilution of 1 to 100.

TABLE I.—STRENGTH OF HEMOTOXIN FROM NEUTRALIZED MILK CULTURES OF BACTERIUM WELCHII.

Whey.		Rabbits blood, 5 per cent.		Hemolysis.
1.00 c.c.	+	1 c.c.	=	Complete.
0.75 c.c.	+	1 c.c.	=	Complete.
0.5 c.c.	+	1 c.c.	=	Complete.
0.25 c.c.	+	1 c.c.	=	Complete.
0.1 c.c.	+	1 c.c.	=	Complete.
0.075 c.c.	+	1 c.c.	=	Complete.
0.05 c.c.	+	1 c.c.	=	Complete.
0.025 c.c.	+	1 c.c.	=	Complete.
0.01 c.c.	+	1 c.c.	=	Partial.
Control, 1 c.c. NaCl 0.75 per cent.	+	1 c.c.	=	Negative.
		Strength, 0.025		(Dilution, 1 to 40)

Stability of the Hemotoxin. The hemotoxin of the gas bacillus is a relatively stabile substance. When kept in the dark at a low temperature the strength of the solution remains fairly constant. Thus a preparation was made about June 15 of the past year which had a strength of 0.025 c.c. (1 to 40). This was used repeatedly for testing sera for about four weeks, during which time it slowly deteriorated until its strength on July 10 was 0.05, a dilution of 1 to 20. This preparation was then put aside and not tested again until October 26, when it had a strength of 0.075, a dilution of about 1 to 13. A similar preparation with a strength of 0.2 c.c. (1 to 5) on December 14, 1918, was tested repeatedly for about five months and on May 7, 1919, its strength was the same.

Production of the Antihemotoxin. The attempt was now made to immunize rabbits with the hemotoxin of the gas bacillus produced by the method described. Six rabbits were given increasing doses of hemotoxin subcutaneously, starting with small quantities

representing low multiples of the hemolytic unit. No definite effect upon the animal's health could be noted. The weight remained stationary and there were no changes at the point of inoculation. As the doses became larger the health of the animals was not appreciably affected, but a good deal of subcutaneous edema and induration developed at the site of inoculation. This edema and swelling were transient, however, and usually disappeared in three or four days. Of the animals originally selected one died of a laboratory infection and one developed subcutaneous abscesses, necessitating its destruction. The other rabbits remained under treatment four months and showed the presence in the blood stream of antihemolytic substances, which could be demonstrated in high dilutions of the serum.

Strength of the Antihemotoxin. The serum of rabbits treated with increasing doses of the hemotoxin of the gas bacillus contains an antihemotoxin for this substance. If the serum be allowed to come in contact with the hemotoxin it neutralizes it completely, so that when blood corpuscles are subsequently added no solution takes place. The usual strength of the antihemotoxin in animals under treatment was about 1 to 1000 when tested against freshly prepared hemolysins, using a hemolytic unit as above described as the index. This is shown in the following table.

TABLE II.—STRENGTH OF ANTIHEMOTOXIN. SERUM FROM RABBIT I TESTED *vs.* A HEMOTOXIN OF UNIT STRENGTH 0.1.

Hemotoxin.	Serum.	Protection.
0.1	0.1 c.c.	+++
0.1	0.08 c.c.	+++
0.1	0.06 c.c.	+++
0.1	0.04 c.c.	+++
0.1	0.02 c.c.	+++
0.1	0.01 c.c.	+++
0.1	0.008 c.c.	+++
0.1	0.006 c.c.	+++
0.1	0.004 c.c.	+++
0.1	0.002 c.c.	+++
0.1	0.001 c.c.	+++
0.1	0.0008 c.c.	+++
0.1	0.0006 c.c.	++
0.1	0.0004 c.c.	++
0.1	0.0002 c.c.	0
0.1	0.0001 c.c.	0
0.1	1 c.c. NaCl 0.75 per cent.	0

Complete protection indicated by +++; partial by ++; slight by +; none by 0.

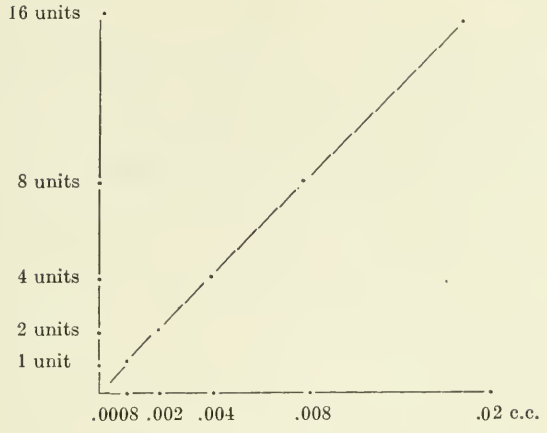
The immune sera were always tested in dilutions of 0.1 c.c. or less. Normal rabbits' serum in higher concentrations, 1 c.c., 0.5 c.c., 0.125 c.c. protects the corpuscles against several multiples of a hemolytic unit, but this reaction appears to depend upon the bathing of the corpuscles in a protective medium rather than upon a true neutralization of the hemotoxin. The protection afforded by normal serum never appears beyond a dilution of 1 to 10. In the serum outlined in Table II the corpuscles were completely protected against the hemotoxin by a quantity of 0.0008 c.c., which represents a dilution of the serum of about 1 to 1250. The usual strength of the antiserum was somewhat less, about 1 to 1000.

Method of Combination. The titration of the antiserum against minimal doses of the hemotoxin, while it offers a simple method of determining its strength, is subject to certain possible errors. The length of time required for solution of the corpuscles by the hemotoxin and for estimating the strength of the antihemotoxin is too long, and in addition the deterioration of the hemotoxin may be such as to make the quantity regarded as the unit incapable of causing a complete solution of the cells. Later, therefore, the sera were always titrated against several multiples of a hemolytic unit, usually against multiples representing 2, 4, 8 and 16 units. Such a series can be read at the end of four hours and in addition gives some information as to the mode of union of the antihemotoxin with the hemotoxin. With fresh preparations the substances combine apparently according to the laws of multiple proportions. This is shown in the following table:

TABLE III.—STRENGTH OF ANTIHEMOTOXIN FROM RABBIT I DETERMINED BY TITRATING AGAINST MULTIPLES OF A HEMOTOXIC UNIT.

Hemotoxin.		Quantity of serum protecting completely.
16 units	1.6 c.c.	0.02 c.c.
8 units	0.8 c.c.	0.008 c.c.
4 units	0.4 c.c.	0.004 c.c.
2 units	0.2 c.c.	0.002 c.c.
1 units	0.1 c.c.	0.0008 c.c.

If this series be put in the form of a curve with abscissas and ordinates it will be seen that the union is represented by practically a straight line thus:



Curve of union.

It is interesting to note in this connection that the antihemolysin produced in animals by the immunization with the hemolysin in fungi also combines with the hemolysin according to the laws of simple multiples, as was shown by Ford and Rockwood.[1]

Combination of Antiserum with Old Hemotoxin. As the hemotoxin deteriorates it loses its strength and its method of combination with the antihemotoxin does not appear to be as simple as when fresh. Larger quantities of antiserum are required to neutralize given quantities of hemotoxin and the line of union with multiples of a hemolytic unit is no longer a straight line but a rapidly ascending curve. The laws governing this union have not been worked out completely, but it apparently follows the same rule as other toxins and antitoxins, and may be explained by the theory that toxoids are formed as the hemotoxic solutions age. This will be taken up in a subsequent publication.

Conclusion. By the immunization of animals with the hemolytic or hemotoxic substance produced in milk by Bacterium welchii, an antihemolysin or antihemotoxin of a strength of 1 to 1000 to 1 to 1250, has now been produced. The demonstration that this substance can act as an antigen offers the final proof that it belongs to the group of true bacterial hemolysins or true hemotoxins.

[1] Mode of Union between the Amanita-Hemolysin and its Antihemolysin, Journa of Pharmacology and Experimental Therapeutics, January, 1913, No. 3, iv, 235.

FURTHER OBSERVATIONS ON THE FUNCTIONS OF THE INTERCOSTAL MUSCLES

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In two former publications[1] the writer sought to show how observations on the respiratory movements of the costal margins give us information which enables one to gain definite conceptions about the conformation of the diaphragm. Briefly stated, the intercostal muscles and the diaphragm are antagonists. The minus barometric pressure produced in the pleural cavity during inspiration is due entirely to the excursion of the ribs and the diaphragm. The costal excursion increases the capacity of the thorax in its anteroposterior and transverse diameters, and the phrenic excursion alone increases the longitudinal diameter of the thorax. If all these muscles are activated at the same moment it is clear that to accomplish an excursion of the ribs and diaphragm the intercostal muscles and the diaphragm must each reciprocally overcome the minus pressure created by the other. The diaphragm must overcome the minus pressure produced by excursion of the ribs before there can be phrenic excursion and the intercostals must overcome the minus pressure produced by excursion of the diaphragm before there can be any costal excursion. The lower six intercostal muscles and the diaphragm are also antagonists in controlling the movements of the costal borders.

Unopposed by phrenic action, the intercostal muscles will cause the entire costal margin to move away from the median line, and unopposed by the intercostals the diaphragm will draw the entire costal margin toward the median line.

[1] Arch. Int. Med., August, 1913, xii, 214; ibid., November, 1917, xx, 711.

If the diaphragm is paralyzed, or its costal attachments are cut away, the outward movement of the costal margin will be greatly exaggerated. If the intercostal muscles are paralyzed then the costal margins will move toward the median line during inspiration.

The intercostal muscles and the diaphragm are antagonists in determining the direction in which the costal margins will move during inspiration, but the direction in which the costal margins may move does not in any way express the intrapleural pressure during inspiration. Nor does the direction in which the costal margins move give expression to the inspiratory excursion of the lung. In other words there may be adequate (not normal) inspiratory enlargement of the lungs in all three dimensions whether the costal borders move in a median or a lateral direction.

Former interpretations of respiratory movements of the costal borders were based on the experiments and interpretation of Duchenne, which considered only the factor of increased intra-abdominal pressure during descent of the diaphragm as the source for lateral movement of the costal borders.

The writer proved by clinical observations and animal experiment that the balance of control over the costal margins depended on the arch of the diaphragm.

In human beings the intercostal muscles have a small margin of superiority over the diaphragm in determining the direction in which the costal margins will move. The more nearly the curve of all or any part of the diaphragm approximates a plane the greater mechanical advantage will that part of the diaphragm have in control of the costal margin to which it is attached. The anteromedian portion of the diaphragm is less arched than its lateral posterior portion, consequently less depression of the anteromedian portion is required to give that part of the diaphragm mastery over the costal margin to which it is attached than is required in the case of the lateral posterior part of the diaphragm.

The phrenic muscle fibers which underlie the pericardial sac, are assigned to the costal margins from the subcostal angle to the eighth cartilage on the costal margin. When all the chambers of the heart are enlarged as in decompensated hearts from myocardial or mitral diseases, and when the pericardial sac is enlarged, then the antero-

median or sternocostal part of the diaphragm is depressed and as a consequence the examiner will see a symmetrical narrowing of the subcostal angle during inspiration, but beyond the eighth costal cartilage the costal margins are seen to move away from the median line during inspiration.

The balance of control over the costal margin is so nicely adjusted and depends so wholly upon the curvature of the diaphragm that any asymmetry of phrenic curve to the two sides of the median line will make itself apparent in asymmetrical movement of the costal margin.

If the left ventricle is enlarged and the right ventricle and right auricle are not greatly enlarged, the left costal margin (to the eighth rib) will move less in an outward direction than the corresponding right side, and the left side may move toward the median line if there is sufficient flattening of the diaphragm. If the right ventricle and right auricle are enlarged, and the left ventricle is not enlarged, then the right costal margin as far as the eighth rib will be restricted in its outward movement, and may indeed move toward the median line with inspiration. So the direction of movement of the subcostal angle and the symmetry or asymmetry of movement of the two sides may be employed to interpret the arch of that part of the diaphragm underlying the pericardial sac, and inferentially we gain valuable evidence concerning the size of the pericardial sac and also evidences of the size of the left ventricle, right ventricle, and right auricle.

The symmetry of movement of the entire costal borders gives evidence of the symmetry of the right and left vaults of the diaphragm. Any condition which will increase the arch of one side of the diaphragm, such as enlargement of the liver or subphrenic abscess, will cause the costal margins to move farther laterally and more promptly than the costal margin of the other side. When the right thorax in one instance was filled with pus which followed rupture of a large subphrenic abscess through the diaphragm, the right costal margin moved further away from the median line during inspiration than did the left margin where the lung was perfectly normal.

The movement of the costal borders is a reliable index of the elevation or depression of the arch of the diaphragm.

When the lung is enlarged by atrophic emphysema or by hypertonus of the bronchiolar musculature, the costal margins are drawn toward the median line during inspiration.

In cases of pneumothorax and empyema, when the under surface of the diaphragm is convexed the costal margin moves away from the median line during inspiration. When air is released or fluid is aspirated, so that the leaf of the diaphragm is no longer convex on its under surface, the costal margin will move toward the median line when the diaphragm is activated, although under such conditions there can be no phrenic excursion.

The movement of the costal margin is determined by the activation and arch of the diaphragm and is not dependent on the excursion of the diaphragm.

The failure to differentiate between evidences of excursion and evidences of activation of the phrenic leaf, and the failure to appreciate the mechanical significance of the diaphragmatic arch, have led to misinterpretation of the action of the diaphragm.

Study of the respiratory movements of the costal margins gives valuable information concerning the conformation of the entire diaphragm and also enables us to recognize any disturbance of balance between the intercostals and diaphragm when the impairment is on the part of the intercostal muscles.

In former years, when evidences of excursion were wanting, the diaphragm was supposed to be paralyzed and no significance was attached to the direction or degree of excursion of the costal margins.

The excursion of the abdominal wall is a measure of the excursion of the diaphragm, but the excursion of the costal margins simply indicates the resultant of the two forces which determine the direction and degree of excursion of the costal margin. These two forces are derived from phrenic and intercostal muscle activation and must not be confused with evidences of excursion of the diaphragm.

The more nearly the phrenic muscle approximates a plane the greater mechanical advantage will it have in procuring mastery of the costal border and the more curved the plane of the diaphragm the less evidence there will be of its activation. It matters not whether the diaphragm is convexed downward as in empyema and pneumothorax, or convexed upward, as in hepatic enlargement or

subphrenic abscess. Although the diaphragm moves upward (in some cases of pneumothorax and empyema) during inspiration, the costal margins of the affected side will move outward during inspiration. This experience, which can be plainly seen with the fluoroscope in patients who have a pneumothorax under positive pressure, very definitely disposes of the old interpretation of inspiratory spreading of the hypochondria which was based on Duchenne's experiments.

Movement of the ribs and the degree and direction of movement of the costal borders give valuable aid in detecting evidences of paresis of intercostal muscles. The costal excursion very faithfully mirrors the excursion of the underlying lung. This is of great importance in physical examinations, for it enables the examiner to detect regional modifications of pulmonary excursion.

By physical examination the doctor should form very definite ideas of the size, density and extensibility of the lungs. Indeed (with the exception of a few adventitious signs) all of our methods of pulmonary examination are directed toward an estimate of these three attributes of the lung. Of the three attributes, viz., size, density and extensibility, the last is the most exquisitely responsive to pathological changes. Extensibility is the first physical attribute of the lung which is modified in all diseases of the bronchi, lung tissue and the pleuræ. It requires only a few moments to palpate the respiratory excursion of all the ribs and determine the character of excursion of the costal margins. When these observations are critically performed the examiner will have formed a definite conception of the conformation of the diaphragm and also a clear idea of the extensibility of the upper and lower lobes of the lungs.

Although paralysis of the intercostal muscles will diminish the vital capacity of the lungs in direct proportion to the extent of the lesion, all paralyses are well tolerated excepting one combination, and that is a paralysis of the upper half of the intercostals when the remaining lower half of intercostal muscles are active.

Case I.—A plump, healthy-looking child, aged two years, was brought to the hospital on account of what seemed to be paroxysms of suffocation. Stenosis of the upper air passages was suspected.

The child lay very comfortably on his back in bed and exhibited

no signs of distress unless he was engaged in play and laughed or cried. Any activity which was attended with an increase of respiration was attended with pronounced cyanosis. Dyspnea and cyanosis were so pronounced it frequently seemed that suffocation was imminent.

Cyanosis and respiratory discomfort increased in a vicious cycle as any incentive to deep breathing was employed. The more deeply and rapidly the child tried to breathe the worse it breathed. There was no prolongation of either expiratory or inspiratory phase. It was also observed that during these violent inspiratory efforts, the upper thorax was violently retracted and the lower thorax was violently distended with exaggerated spreading of the hypochondria and protrusion of the abdomen. There was a genuine see-saw between the upper and lower thorax. The scaleni were intact as evidenced by fixation of the first rib of each side and a want of descent of the manubrium during inspiration. During an inspiratory effort the ribs on both sides from the second to the sixth inclusive were strongly retracted. The seventh rib (on both sides) was stationary. From the eighth rib to the twelfth (inclusive) there was an exaggerated excursion in a normal direction.

It was clearly evident in this case there was a marked diminution in volume of the upper lung and exaggerated distention of the lower lung during a violent inspiratory effort; consequently the lower lung was distended in part by air which was displaced from the upper lung during inspiration, so the patient was ventilating his lower lung in large part by alveolar air from the upper lung, and during expiration alveolar air from the lower lung was driven into the upper lung. There was a reciprocal expansion and contraction between the upper and lower lung. During strong inspiratory efforts, alveolar air was shunted back and forth between the upper and lower portions of both lungs. Tranquil breathing was attended with adequate ventilation, but forced breathing developed a vicious reciprocal contraction and expansion between the upper and lower parts of both lungs which caused intense air hunger and cyanosis.

There were no physical signs to indicate any disease of the bronchial tract, or lung parenchyma, or pleuræ.

A skiagram revealed marked signs of tubercular disease of the

bodies of the upper six dorsal vertebræ. In other respects the *x*-ray revealed a perfectly normal thorax.

There were no other neurological signs obtainable which would indicate any disease of the spinal cord or the intercostal nerves. However, the respiratory distress and inspiratory retraction of the second to the sixth ribs (inclusive), associated with the disease of the vertebræ revealed by the *x*-ray, seemed to justify a diagnosis of motor paralysis of the intercostal muscles which normally accomplish the ventilation of the upper parts of the lungs.

The vicious cycle of rebreathing established between the upper and lower lung was due to the flexibility of the child's ribs as well as to the motor paresis of the upper intercostal muscles. Had the same extent of motor paralysis occurred in an older person with more resistant ribs there would probably have been little or no respiratory distress. This is the only occasion in which I have seen paralysis of the upper intercostals when the lower intercostals were active, and it is the only kind of intercostal paralysis which will cause reciprocal rebreathing between two regions of the lungs. I have frequently seen paralysis of the lower intercostal muscles when the upper muscles were intact, and on one occasion motor paralysis of all the intercostal muscles with scaleni and diaphragm intact, but the patients had no respiratory distress because there was no rebreathing between different parts of the lung.

Paralysis of all intercostal muscles on one side is also well tolerated.

Case II.—A little girl, aged about six years, was brought to the hospital directly after she had fallen on to the ground from a ladder on which she was climbing. The resident physician palpated what he interpreted as the body of the third cervical vertebra projecting into the posterior pharyngeal wall. The projecting mass was pushed back into position. It was then discovered that the child had motor paralysis of the left upper and lower extremities, and it was also observed that the left side of the thorax did not move with respiration. A lumbar puncture revealed a large amount of free blood in the subarachnoid space. There was complete paralysis of all the intercostals of the left side of the thorax, and there was no demonstrable evidence of any activation or excursion of the left side of the diaphragm. All the pulmonary ventilation was accomplished by the intercostals and diaphragm of the right side.

The child was not cyanotic, she had no air hunger, and there was no inspiratory retraction of the left thorax. The entire left thorax was completely immobilized. There must have been some ventilation of the left lung because there would certainly have been cyanosis at least, had all the blood passing through the left pulmonary veins been unrespired blood. A very moderate increase in respiratory movement of the normal right lung would have compensated for an increase of CO_2 contributed to the aortic blood by unrespired blood from the left lung, but superventilation of the right lung could not prevent cyanosis from appearing under such circumstances. We would have seen the same degree of cyanosis which appears in fibrinous pneumonia of the entire left lung. Were there no ventilation of the left lung under such conditions as presented in this child, then the only area for the escape of CO_2 and absorption of oxygen for the left lung would have been the cross-section of the left bronchus.

When we consider the estimated area of the total respiratory membrane of an adult lung to be ninety square meters, it is apparent that although a bronchus to a lung may be open, it offers a negligible area for transpiration of gases. In the case of this child with all the intercostal muscles and diaphragm of the left side paralyzed, the only manner in which anoxemia could have been prevented would have been through some respiratory excursion of the mediastinum, for there certainly was no respiratory excursion in a longitudinal or anteroposterior diameter. There must have been some respiratory movement in the third dimension. With the disturbance of equilibrium between the right and left pleural cavities which attended intercostal and pleural excursion of the right side the mediastinal structures moved toward the right. In this manner the transverse diameter of the left pleural cavity was enlarged during inspiration and diminished during expiration. There was therefore no rebreathing between any two portions of the lung.

To summarize. Paralysis of all the intercostal muscles, of both sides, or of one side, or the lower half of both sides, or the lower half of one side, produces no respiratory distress or cyanosis when the patient is at rest.

Paralysis of the upper half of the intercostals of both sides, how-

ever, produces severe respiratory distress when the ribs are sufficiently flexible to admit of reciprocal expansion and contraction between the upper and lower parts of the lungs so as to cause rebreathing between the upper and lower lung.

Although this manner of intercostal paralysis is the only kind which will *per se* produce suffocative symptoms, intercostal paralysis of a moderate extent will diminish the vital capacity of the lung. A patient suffering from syringomyelia of the cervical and dorsal cord, had very moderate emphysema which was not sufficient to cause flattening of the diaphragm but the pulmonary volume was enlarged so that the lower border of the lung stood one intercostal space lower than is normally found. The striking feature about this patient was the very small margin of cardiorespiratory reserve, which was disproportionately small for the very moderate emphysema. Physical examination and the *x*-rays both failed to show any signs of lung or heart disease which could in any way explain the small vital capacity of the lung, which was only 1100 c.c.

Pulmonary emphysema, which would reduce the vital capacity to so small an amount, must be a severe emphysema, and this man did not have severe emphysema, nor was there any evidence of cardiac enlargement or stasis in the pulmonary circulation, or other disease of the bronchi, lung parenchyma, or pleuræ. The striking disparity between the moderate emphysema and great reduction in the vital capacity could be accounted for only by evidences of paralysis of the intercostal muscles from the third to the seventh (inclusive) of the left side. The left costal border from the subcostal angle to the eighth rib was drawn toward the median line during inspiration. The left costal margin below the eighth rib and the entire right costal margin moved laterally during inspiration. When the ribs of the left side were palpated successively from above downward, all could be felt to move normally excepting the fourth to the eighth, which on palpation revealed inspiratory retraction.

There was no evidence of disease of the underlying lung, and there was not merely a want of normal excursion of these five ribs, but there was a genuine retraction of the ribs during inspiration.

The retraction of the costal border of the left side from the angle to the eighth costal cartilage was explained by the normal diaphragm

in this region being unopposed by intercostal muscles. Further confirmation of this interpretation of the small vital capacity was found in evidences of marked paresis of the abdominal muscles of the left side. During expiration the abdominal wall was seen to be rotated on a longitudinal axis; the median line was drawn toward the right side during forced expiration, and the umbilicus moved upward and toward the right when the patient coughed.

During the act of coughing one could palpate an equal bursting tension over the left and right sides of the abdomen, but the abdominal wall to the left of the median line was clearly seen to be protruded, but the right side was retracted. To the left of the median line the abdominal wall was passively distended, but to the right of the median line the abdominal wall was actively contracted when the patient coughed or made a forced expiration.

An analysis of this patient's peculiar respiratory limitations and movements became quite clear when the movements of the costal margin were employed to study the balance of power between the diaphragm and the intercostal muscles, but aside from this point of view his respiratory movements became a hopeless tangle.

In several cases of syphilis of the spinal cord it has been possible to demonstrate paralysis of several groups of intercostal muscles by observing the respiratory movements of the entire costal margin. Where the diaphragm is unopposed by intercostal muscular action the costal border will be drawn toward the median line during inspiration; but the retraction of the costal border does not prove there is impaired muscular power of the intercostal muscles, the intercostal muscles may be normal and the costal margin be retracted because flattening of that particular part of the diaphragm gives the phrenic muscle mastery over the costal end. When retraction of the costal margin is an evidence of paresis or paralysis of the intercostal muscle, then the involved rib will be seen to retract throughout its course, whereas the anterior end of the rib will be retracted and the rib in its course will be normally elevated when flattening of the phrenic arch is responsible for retraction of the costal border.

In studying the respiratory excursion of the ribs one must differentiate between the significance of excursion of the costal ends

(viz., the costal border) and excursion of the arcs of the ribs. Direction of the excursion of the ends of the ribs (costal border) is quite independent of excursion of the diaphragm and excursion of the arc of the rib. The costal border (rib ends) will move either toward the median line or laterally as the pull of the diaphragm or intercostal muscle may have the mastery of the ends of the ribs. When the intercostal muscles are paretic or paralyzed the costal border formed by the ends of the affected ribs will be drawn toward the median line during inspiration, and the arc of the affected ribs will also be retracted during inspiration.

When the diaphragm is flattened and the intercostal muscles are normally activated then the costal border will be drawn toward the median line during inspiration, but the course of the rib will move in the normal "bucket handle" arc.

Careful study of the respiratory excursions of the arcs of the ribs and the costal border gives very valuable information on the innervation of the diaphragm and the intercostal muscles. By this study we are also enabled to visualize the conformation of the leaves of the diaphragm and by such observations we also gain valuable information about the extensibility of the lung.

Costal movements accurately mirror the movements of the underlying lung.

When the respiratory excursions of the thorax is studied in this manner the lung and its bounding walls take on an entirely new significance.

The lung will be appreciated as a very lively organ which has a motility quite different from the popular conception of an elastic bag which is alternately expanded and contracted as a whole, in obedience to changes of barometric pressure within the pleural cavity.

A NEW METHOD FOR TESTING IMMUNITY BY MEANS OF WHOLE BLOOD, WITH SPECIAL REFERENCE TO PNEUMONIA AND ITS PROPHYLAXIS BY BACTERINATION

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AND

GEORGE D. HEIST, M.D.

(ABSTRACT)

The requirements for a workable and dependable test for immunity are: (1) it must be demonstrative; (2) it must also demonstrate susceptibility; (3) its results must be conclusive as to the individual, and not dependent upon massive exposures and statistics; (4) it must involve no risk to the individual, whether animal or man; (5) it must be simple and easy of performance; (6) it must be sufficiently delicate. The method to be described appears to possess these requisites insofar as applies to the microörganisms thus far studied by this technic. How far its scope extends can be determined only by observation. With pneumococci (Type III specially) it is more sensitive than agglutination.

It depends upon a certain bactericidal power resident in whole, coagulable blood; but not in any fraction thereof, and not in citrated blood. This power is specific. Microörganisms pathogenic for a species flourish in the whole blood of normal individuals of that species; while organisms non-pathogenic for the species perish, or fail to develop in a given time. Stated conversely, failure of a microörganism pathogenic to certain species and blood-viable, to grow in the blood of certain other species, indicates natural immunity of the latter.

The same is true as to acquired immunity of individuals. The

whole blood of an individual possessing induced immunity toward a microörganism pathogenic to the species, will kill, or greatly retard the growth of, that microorganism.

We wish not to be misunderstood as asserting that the phenomena reported *explain* immunity—they *accompany* it and are thus facts to be considered in any explanation; but at present we are dealing merely with their value as *indices*.

These facts came to light in the course of a research previously partially reported upon to the Association[1] and directed toward finding the poisons responsible for the toxemic complex of lobar pneumonia, and determining why quinin prevents crisis and promotes recovery by lysis. At a point in this study, it seemed desirable to investigate the blood reactions of cinchonized and uncinchonized animals and men, including pneumonia patients, convalescents, bacterinated individuals, and normal individuals. Except for the constant destruction of pneumococci by the serum of sufficiently cinchonized individuals, the results with serum, citrated blood, defibrinated blood and isolated corpuscles were either negative or inconsistent; and we sought to use whole, unaltered blood. Professor Benjamin F. Lacy,* of the Central High School of Philadelphia, solved the bactericidal and immunity problem of this investigation by suggesting the utilization of *capillary attraction* and *surface tension*.

The object is to take but a small quantity of blood, as nearly as possible in the state in which it circulates. To emphasize this, we speak of it as "unaltered blood," as "coagulable blood," as "whole blood," as "flowing blood," as "living blood"—according to the requirements of the context. It demands simple manipulations, completed quickly. The tip of a capillary glass pipette is touched to the surface of a broth culture and the fluid permitted to flow up to a mark. The tip of the tube is then touched to moist cheesecloth, when the fluid runs out, leaving, however, a film containing microörganisms, sticking to the glass. The tip is now introduced into a drop of blood obtained by pricking a finger or vein (or, in the case of chickens, from the heart). The blood flows up the seeded tube to the mark and covers the film. The tube is sealed and incubated (with controls) for twenty-four hours. The

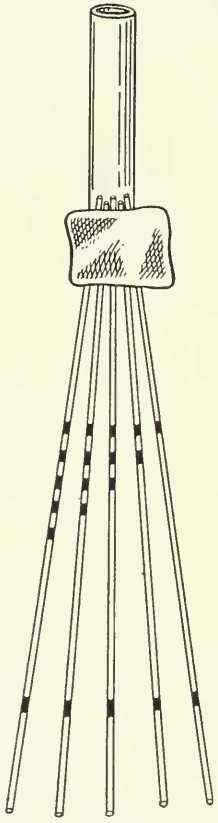
* Dr. Heist worked out the technic. Hence I call it *the Lacy-Heist* method.—S. S. C.

tip is then broken off and a smear made from the contained blood, which has, of course, coagulated. Whether coagulation in the tube favors or hinders the phenomena interpreted as indices of immunity, we do not know. The negative result of Barber's[5] experiment with the hanging drop hint at a favoring influence, but the question is still open. We hope to find some means of preventing it, without introducing a new source of error. For the present, we accept it as an incident.

Pigeons and chickens are naturally immune to the pneumococcus; mice and rabbits susceptible. When the blood of mouse or rabbit is compared with the blood of chicken or pigeon, striking differences appear. In the tube filled with mouse or rabbit blood, the pneumococci grow abundantly; in the tube containing pigeon or chicken blood they fail to grow. That the action is bactericidal, and not merely inhibitory, may be shown by blowing out the contents of the tube into broth and incubating. No growth results. Similar results are obtained with the globoid bodies associated with acute anterior poliomyelitis. These grow in the blood of susceptible children, but in the blood of rabbits, which are not susceptible to poliomyelitis, they die. Kolmer and Matsunami,[3] using our method, found likewise that meningococci would not grow well in the blood of the naturally immune rabbit; but flourished in the blood of the susceptible mouse.

To measure this bactericidal power we used serial dilutions of cultures, by means of a modification of Wright's many-stemmed pipette[4] for observing coagulation time. We found that in measuring either natural or induced immunity the virulence of the strain is of utmost importance; and that no contamination by saprophytic bacteria occurs. Experiments were made to explain this. Small numbers of strictly non-pathogenic bacteria, such as Bacillus subtilis, seeded in the whole blood of any species, failed to grow; while the bacillus of mouse typhoid, which is extremely virulent for mice and rabbits, grows well in the blood of both species. Strains of avirulent pneumococci failed to grow in the blood of normal rabbits unless the tubes were seeded from suspensions containing large numbers; while strains of high virulence grew in the blood of the same rabbits even when very few pneumococci were seeded. To express this differently, the blood of normal rabbits is able to kill

large numbers of pneumococci that have lost their virulence through long cultivation upon artificial media, but is powerless to kill even scanty numbers of virulent pneumococci. It seems a safe analogy



Modification of Wright's many-stemmed pipette used in estimating the bactericidal power of whole blood.

to say that if a strain of pneumococci grows well in human blood it is virulent for human beings, and that a strain which does not grow well in human blood is not virulent for human beings.*

Thus, we have a method by which to test the virulence of any

* This suggests also the possibility of utilizing the attenuation of artificial culture—as Jenner used the attenuation of culture on the cow—to induce immunity with living, instead of dead virus. Experiments are under way, but we invite parallel observation by others. Individual immunity to the immunizing strain being demonstrated, there should be no risk.

strain of microbes without risking the life of man or animal. Having a strain proved virulent, its failure to grow within a given time in the blood of any individual would point to immunity. The results of bacterination methods may thus be tested without danger and without waiting for an epidemic with massive exposures. Our experiments on animals tend to confirm this view.

I. VIRULENCE AND ITS RELATION TO ABILITY TO GROW IN BLOOD IN VITRO

The fact that avirulent pneumococci fail to grow in the blood of normal rabbits suggests the question: Is an increase of virulence accompanied by an increased ability to grow in blood?

We had a culture of Type III pneumococci moderately virulent for mice but not for rabbits. The ability of this strain to grow in the whole blood of normal rabbits was tested on five animals. A 1 to 16 dilution of broth culture was the highest dilution producing growth (Table I). This strain

TABLE I

THE GROWTH OF TYPE III PNEUMOCOCCI, AVIRULENT FOR RABBITS, IN THE WHOLE BLOOD OF NORMAL RABBITS

Rabbits.	Dilutions of twelve-hour blood broth culture.				
	Undiluted.	1 to 4	1 to 16	1 to 64	1 to 256
1	−	+	−	−	−
2	+	+	−	−	−
3	+	+	+	−	−
4	+	+	−	−	−
5	+	−	+	−	−

THE GROWTH OF THE SAME STRAIN AFTER PASSAGE THROUGH FIFTEEN MICE AND THREE RABBITS

Rabbits.	Dilutions of fourteen-hour blood broth culture.				
	to 100	1 to 1000	1 to 10,000	1 to 100,000	1 to 1,000,000
1	+	+	+	−	−
2	+	+	+	+	−

was passed through 15 mice and 3 rabbits. Growth was then obtained from a dilution of 1 to 100,000. In other words, when the pneumococci were avirulent for rabbits it required a very heavy seeding to start growth in rabbit's blood, whereas when the pneumococci were virulent very few sufficed.

These experiments show clearly the correlation between the virulence of pneumococci and their ability to grow in whole blood *in vitro*.

II. THE PRODUCTION OF ANTIBODIES IN WHOLE BLOOD BY BACTERINATION

Two questions presented in connection with the test of the bactericidal activity of whole blood are: (1) Does the reaction appear in the blood before the agglutinins may be found in the serum, and (2) can the test be made to serve as a quantitative measure of the immunity produced by pneumococcal (and other) inoculations? These questions we have endeavored to answer.

EXPERIMENTS UPON RABBITS WITH TYPE I PNEUMOCOCCI

Type I pneumococci were grown for fourteen hours in infusion broth containing 1 per cent. glucose. The medium was then heated for half an hour to 53° C.; the organisms removed with the centrifuge, suspended in normal salt solution, heated to 55° C. for a half hour; and 0.3 per cent. tricresol added. Counts were made by Wright's method. Inoculations of this bacterin were given intravenously. Tests of the bactericidal action of the blood of the rabbits were made before the inoculations were begun and at frequent intervals thereafter. Only the first and last tests need be given (Table II). Agglutinations were also performed with the serums of these rabbits before and after the inoculations.

TABLE II.—TYPE I PNEUMOCOCCI

BEFORE INOCULATION

Rabbits.		Dilutions of eleven-hour blood broth culture.		
		1 to 125	1 to 625	1 to 3125
C	.....	+	+	+
C2	.....	+	+	+
C3	.....	+	+	+
C4	.....	+	+	+
Control . .	.....	+	+	+

AFTER THREE INTRAVENOUS INOCULATIONS

Rabbits.	Total dosage.	Dilutions of ten-hour blood broth culture.		
		1 to 125	1 to 625	1 to 3125
C	60,000,000	+	−	−
C2	240,000,000	−	−	−
C3	600,000,000	−	+	−
C4	1,200,000,000	−	−	−
Control . .	None	+	+	+

After the completion of the inoculations the serum of the two rabbits, C and C2, did not agglutinate pneumococci and yet their whole blood was distinctly bactericidal.

EXPERIMENTS UPON RABBITS WITH TYPE II PNEUMOCOCCI

Three different vaccines prepared from Type II pneumococci were used on this series of rabbits.

A rabbit was infected intraperitoneally with a massive dose of Type II organisms. Just before death the peritoneal cavity was opened under chloroform with aseptic precautions, and washed out with sterile 1 per cent. salt solution. This yielded 50 c.c. of a suspension containing one billion pneumococci per cubic centimeter. The cells were thrown down by slow centrifugation and the supernatant fluid drawn off and heated to 53° C. for twenty minutes, phenol (0.5 per cent.) being added to complete sterilization. This bacterin was used on one rabbit lettered "P." Lieutenant-Colonel Whitmore supplied us with lipovaccine prepared from Type II pneumococci in the Army Medical School, which was used on a second rabbit lettered "L." H. K. Mulford Company supplied us with vaccine made in the usual way from several strains of Type II and suspended in normal salt solution. This was used upon a third rabbit lettered "M." All three vaccines were given subcutaneously. The dosage and results of the first and last bactericidal tests are given in Table III. Twenty-eight days

TABLE III.—TYPE II PNEUMOCOCCI

BEFORE INOCULATION

Rabbits and bacterin inoculated.		Dilutions of twenty-four-hour blood broth culture.		
		1 to 25	1 to 125	1 to 625
P (Washings from peritoneum of mouse)	.....	+	+	+
L (Lipovaccine)	.....	+	+	+
M (Salt solution suspension)	.....	+	+	+
Control . .	.....	+	+	+

AFTER THREE SUBCUTANEOUS INOCULATIONS

Rabbits.	Total dosage.	Dilutions of eighteen-hour blood broth culture.		
		1 to 25	1 to 125	1 to 625
P	5,000,000,000	−	−	−
L	23,000,000,000	+	+	+
M . . .	9,000,000,000	+	−	−
Control . .	None	+	+	+

after the last inoculation the rabbits "P" and "M" showed a very slight or doubtful agglutination, whereas the bactericidal action of their blood was quite marked and appeared much earlier. The blood of rabbit "L" showed no bactericidal action, and its serum did not agglutinate pneumococci.

This experiment shows that bactericidal action for Type II pneumococci may be produced in the blood of rabbits as well as for Type I, and that with this type also, the bactericidal test is more sensitive than the agglutination test. It further shows that a killed bacterin made from pneumococci grown in the living body is superior in immunizing properties to one made from pneumococci grown on artificial media.

EXPERIMENTS UPON RABBITS WITH TYPE III PNEUMOCOCCI

The experiments in which Type III pneumococci were used are the most important of the series because of the difficulty of producing a serum that will give satisfactory agglutination of Type III organism, and because of the difficulty of producing any antibody response whatever in man, by inoculations of vaccine which are well tolerated.

A Rockefeller strain, A 66, was used for Type III experiments. The virulence of this strain was increased and demonstrated as previously stated. The bacterin was prepared from organisms grown in broth and was

TABLE IV.—TYPE III PNEUMOCOCCI

BEFORE INOCULATION

Rabbits.		Dilutions of fourteen-hour blood broth culture.			
		1 to 25	1 to 125	1 to 625	1 to 3125
C5	.....	+	+	+	+
C6	.....	+	+	+	+
C7	.....	+	+	+	+
C8	.....	+	+	+	+
Control . .	.....	+	+	+	+

ELEVEN DAYS AFTER ONE INTRAVENOUS INOCULATION

Rabbits.	Dose.	Dilutions of twelve-hour blood broth culture.			
		1 to 25	1 to 125	1 to 625	1 to 3125
C5	100,000,000	−	±	+	−
C6	500,000,000	−	−	−	−
C7	1,000,000,000	+	+	−	−
C8	2,000,000,000	+	−	−	−
Control . .	None	+	+	+	+

given in a single intravenous inoculation. Table IV shows that a distinct bactericidal action had been induced in the blood of the animals eleven days later. No trace of agglutination was found in the serums of these animals either before or after the inoculation. In considering this experiment as well as those in which Types I and II were used it must be remembered that our object was not to produce the maximum amount of bactericidal action but to find how small an inoculation of bacterin would give demonstrable bactericidal power.

Type III pneumococci are thus shown to be as susceptible to the bactericidal action of immune blood as are Types I and II. As in the case of Types I and II the bactericidal action appears in the blood in measurable quantity before the appearance of agglutinins in the serum.

CONCLUSIONS. 1. Whole, coagulable blood *in vitro* possesses bactericidal—or marked inhibitory—properties which do not appear in blood serum or defibrinated or citrated blood.

2. Increasing the virulence of pneumococci for rabbits increases their ability to grow in rabbit's blood *in vitro*. The mathematical expression of the ability of a strain of pneumococci to grow in the blood of normal rabbits *in vitro* in a given time, is an expression of the virulence of that strain for rabbits.

3. The bactericidal activity on pneumococci of the whole blood of inoculated rabbits is a more sensitive test of immunity than is agglutination. This is especially significant with Type III.

4. The test has an approximate quantitative value. Whether or not it can be successfully applied to the measurement of natural and artificial immunity in man can be determined definitely only by observation.

5. A bacterin prepared from pneumococci washed from the peritoneal cavity of a rabbit dying of pneumococcal infection is more powerful as an immunizing agent for rabbits than one prepared from pneumococci grown on ordinary culture media.

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3. Matsunami, T., and Kolmer, J. A.: Jour. Immunol., 1918, iii, 201 seq.
4. Technic of the Test and Capillary Glass Tube, Constable, London, 1912.
5. Barber, M. A.: Jour. Exp. Med., 1919, vi, 589 seq.

THE RAPIDITY AND PERSISTENCE OF THE ACTION OF DIGITALIS ON HEARTS SHOWING AURICULAR FIBRILLATION

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The fact that digitalis requires many hours or even days to affect the heart when given in the usual doses, has been perhaps the chief disadvantage in the use of the drug in cases of heart disease in which prompt action is urgently indicated. It is well known that repeated doses must be given before the action of the drug manifests itself, and it is often difficult to determine accurately when the action begins. There has also been considerable discussion as to how long the drug remains effective after its administration is stopped, a point of important bearing on the so-called cumulative action of the drug.

In order to gain further knowledge regarding these questions, the effect of large single doses of digitalis has been observed on a selected group of patients suffering from a form of cardiac disorder which is definitely influenced by the drug. All the cases studied were demonstrated by electrocardiograms to suffer from either auricular fibrillation or auricular flutter, and in all the ventricular rate was abnormally rapid. Care was taken in every case to make sure that the patient was not under the influence of digitalis when the large dose was administered, either by the history, or the statement of the physician sending the patient into the hospital, or by a period in the hospital of at least ten days without the administration of the drug.

Digitalis was given by mouth in the form of the tincture and the dose was regulated according to the method worked out by Eggles-

ton.[1] The underlying principle of this method is to give in one or several frequent doses the entire amount of the drug which may be expected to produce the maximum therapeutic effect. The tincture of digitalis used was purchased from a reliable manufacturer and

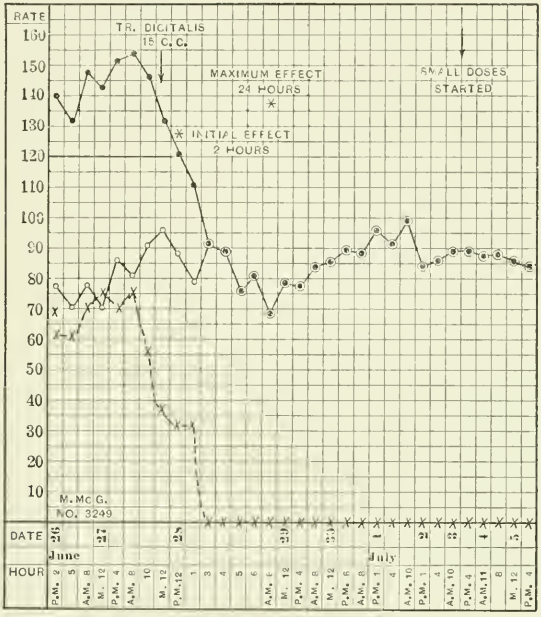

Chart I.—Case 9 of Table. Mitral stenosis and auricular fibrillation. The upper solid line indicates the heart-rate counted by means of the stethoscope placed over the apex-beat. The lower solid line indicates the radial pulse-rate. The broken line indicates the pulse deficit or the number of cardiac contractions that could be heard per minute, which produced no palpable pulsation in the radial artery. The time when the single dose of digitalis caused the initial and maximum effects is indicated. The increase in the rate of the radial pulse and the fall in the pulse deficit with the decrease in the heart-rate are well shown. Initial effect in two hours. Maximum effect in twenty-four hours. Duration of effect not determined.

each lot of the drug was standardized by the "cat method," described by Hatcher and Brodie.[2]

It was found that 1 c.c. of the tincture injected intravenously was approximately the lethal dose for one kilo of body weight of the cats used, and following Eggleston's results, 0.15 c.c. was given

[1] Digitalis Dosage, Arch. Int. Med., 1915, xvi, 1.
[2] Biological Standardization of Drugs, Am. Jour. Pharm., 1910, lxxxii, 360.

for each pound of body weight of the patients. The dose, amounting to 15 c.c. per hundred pounds, was the maximum, and was usually given as a single dose, although in some of the earlier cases the dose was divided into three or more parts and given four to six hours apart. The clinical results obtained in giving large single doses of the drug to about 100 patients have been convincing of the correctness of Eggleston's work. This will be demonstrated also

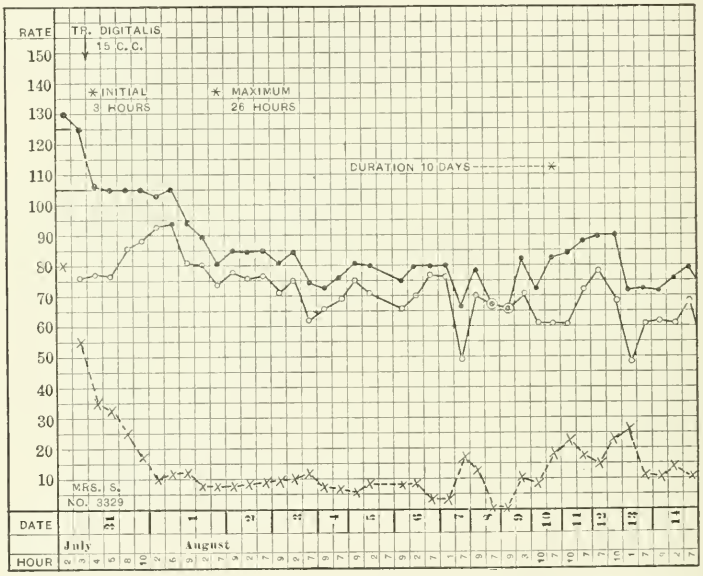

CHART II.—Case 11 of Table. Mitral stenosis and insufficiency, chronic myocarditis and auricular fibrillation. The three lines have the same significance as those in Chart I. The time when digitalis began to be ineffectual is indicated by the increase in the heart-rate which began ten days after the administration of digitalis. Initial effect in three hours. Maximum effect in twenty-six hours. Duration of effect ten days.

by the cases tabulated in this paper. The doses usually ranged from 15 c.c. to 25 c.c. of the tincture.

The patients forming the basis of this paper were studied during continuous rest in bed. The heart rate was counted several times a day by a member of the medical staff, using the stethoscope over the heart, for a number of days whenever the withholding of the drug seemed justified. The radial pulse was also counted, and

these findings, together with the pulse deficit (the difference between the heart and radial rates), were charted. After the digitalis was given similar counts were frequently made, in some cases at fifteen-minute intervals, for several hours. The results of three observations are shown in the accompanying charts.

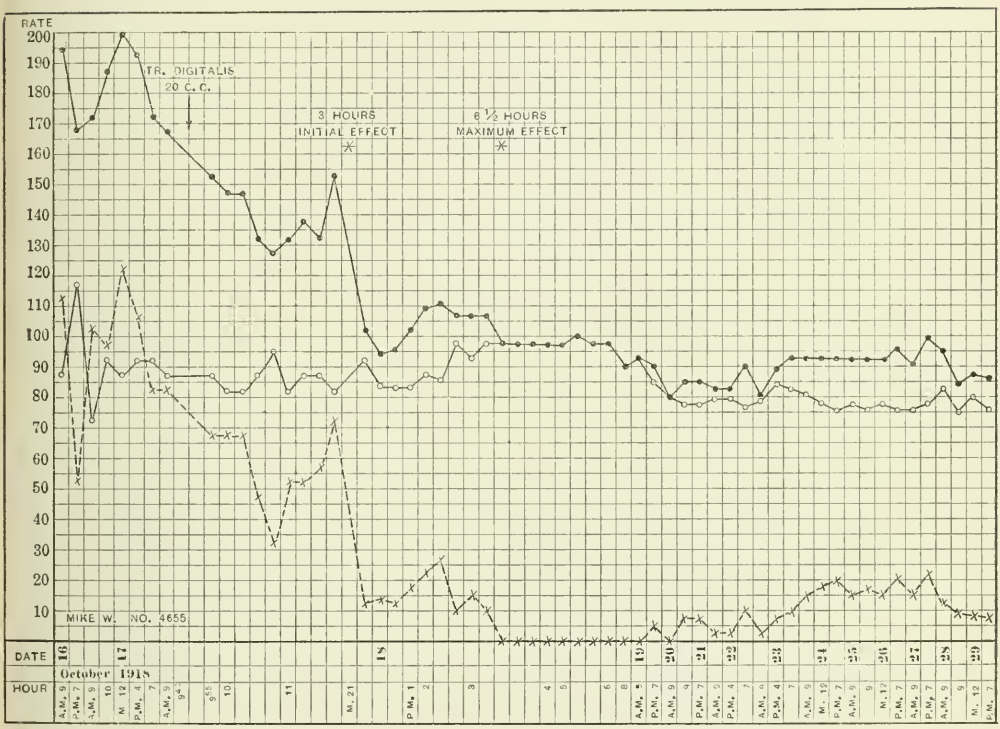

CHART III.—Case 25 of Table. Syphilis, chronic myocarditis and aortitis. The three lines have the same significance as in Chart I. Single dose of 20 c.c. of the tincture given. Initial effect in three hours. Maximum effect in six and a half hours. Heart-rate remained slow for twenty-two days.

The well-known effect of digitalis in slowing the ventricular rate in cases of auricular fibrillation was used as indicating the action of the drug, and practically all of the cases included in this paper showed an abnormally high ventricular rate before digitalis was given. Two cases of auricular flutter are exceptions to the foregoing procedure, and here the disappearance of flutter, as demonstrated

	No.	Sex.	Age.	Wt.	Diagnosis.	Dose.	Heart-rate.			Duration.
							Before.	Onset time.	Maximum effect.	
1	2608	M.	62	124	Arterial sclerosis; mitral insufficiency; chronic nephritis	17 c.c.	85	?	60, 24 hr.	7 days.
2	2178	F.	52	127	Arterial sclerosis; mitral insufficiency; chronic nephritis	18.5 c.c. in 4 doses	120	?	80, 20 hr.	8 days small doses started.
3	2567	M.	48	172	Mitral stenosis and insufficiency	22 c.c. in 3 doses	160	106, 13 hrs.	80, 23 hr.	10 days.
4	2484	F.	49	151	Mitral stenosis and insufficiency; chronic nephritis	22 c.c. in 3 doses	112	105, 5 hrs.	92, 24 hrs.	6 days small doses started.
5	2589	M.	57	190	Mitralinsufficiency; myocarditis; chronic nephritis	29 c.c. in 3 doses	135	?	76, 15 hrs.	3 days small doses started.
6	2819	M.	72	137	Arterial sclerosis; chronic nephritis	15 c.c. in 3 doses	130	?	90, 24 hrs.	8 days small doses started.
7	3115	F.	45	140	Myocarditis; chronic alternans; auricular flutter	20 c.c.	148	102, 3¼ hrs.; flutter changed to fibrillation	90, 24 hrs.	13 days.
8	3132	M.	63	110	Arterial sclerosis; chronic nephritis	6 c.c.	132	80, 3 hrs.	80, 3 hrs.	5 days small doses started.
9	3249	F.	35	106	Mitral stenosis	15 c.c.	145	120, 2 hrs.	68, 24 hrs.	5 days small doses started.
10	3257	M.	57	138	Arterial sclerosis; myocarditis; chronic nephritis	9.5 c.c. 5 days after 19 c.c.	Flutter replaced by normal		rhythm in 3½ hrs.	after 9 days in hospital.
11	3329	F.	36	100	Mitral stenosis and insufficiency; myocarditis	15 c.c.	130–140	105, 3 hrs.	80, 26 hrs.	11 days.
12	3358	F.	47	110	Mitral stenosis and insufficiency; cystic goitre	15 c.c.	130–160	110, 3 hrs.	85, 22 hrs.	8 days.
13	3466	M.	54	156	Arterial sclerosis; myocarditis	10 c.c., 5 c.c., 3 days later	120	?	82, 18 hrs.	13 days after 2d dose.
14	3494	M.	37	135	Mitral stenosis and myocarditis	20 c.c.	120–150	?	84, 20 hrs.	5 days, 2d dose given.
15	3530	F.	49	130	Exophthalmic goitre; myocarditis	20 c.c.	110–125	?	95, 24 hrs.	6 days.
16	3741	F.	43	178	Mitral insufficiency	18 c.c.	112–160	90, 5 hrs.	80, 8 hrs.	2 days mechanism became normal.
17	3757	M.	49	139	Arterial sclerosis; myocarditis; mitral insufficiency	20 c.c.	120	108, 3 hrs.	87, 14½ hrs.	9 days, 2d dose given.
18	3937	F.	42	122	Mitral stenosis and insufficiency	15 c.c.	75–135	60, 3 hrs.	38, 21 hrs.	15 days.
19	4018	F.	60	74	Mitral stenosis and insufficiency	6 c.c.	150–165	114, 2 hrs.	100, 21½ hrs.	4 days death.
20	4102	F.	23	132	Mitral stenosis and insufficiency; aortic stenosis	6 c.c.	95–115	80, 2 hrs.	55, 6 hrs.	10 days patient discharged
21	4190	M.	62	121	Myocarditis and chronic nephritis	15 c.c.	120–128	?	91, 8 hrs. 81, 26 hrs.	9 days patient discharged
22	4230	F.	54	198	Arterial sclerosis; myocarditis; chronic nephritis	10 c.c. 2d dose 10 c.c.	175–180 150–175	160, 4½ hrs. 105, 5 hrs.	120, 22½ hrs. 90, 18 hrs.	30 hrs., 28 hrs.
23	4261	M.	42	168	Myocarditis; syphilis	15 c.c.	120–150	?	70, 24 hrs.	4 days.
24	4449	M.	40	120	Mitral stenosis and insufficiency	20 c.c.	135–160	118, 3 hrs.	112, 7 hrs.	6 days.
25	4655	M.	48	165	Myocarditis; syphilis; aortitis	20 c.c.	167–207	102, 3 hrs.	96, 6½ hrs.	22 days patient discharged
26	4977	F.	37	?	Mitral stenosis and insufficiency; myocarditis	15 c.c.	130–140	110, 2¼ hrs.	70, 9 hrs.	4 days patient discharged.

by electrocardiograms, was taken as evidence of digitalis action. Twenty-six cases were studied and tabulated.

In 16 cases the observations were made at intervals sufficiently frequent after the single dose of the drug was given to determine accurately the time when the digitalis became effectual. The drug was considered to have affected the heart when the ventricular rate first became slower than it had been at any time previous to the administration of digitalis and when the ventricular slowing continued, so that the rate of the ventricles assumed a definitely new level. In 2 cases the permanent disappearance of auricular flutter was taken as the indication that the drug had affected the heart. In all of the 16 cases so observed the heart was affected by digitalis in from two to five hours after the oral administration of a single large dose of the tincture.

The maximum effect of digitalis was considered to have occurred when the ventricles attained approximately their slowest rate and when the pulse deficit had disappeared or reached its lowest count. It was usually quite clear when the maximum effect occurred, but in some cases in which frequent heart-rate counts were not carried on long enough the maximum effect can only be approximated. The charts from the 26 cases studied indicate there is some difference in the length of time required for a single large dose of digitalis to produce the maximum effect on cases of auricular fibrillation, and the cases fall into two groups.

In the first group of 19 cases the maximum effect of the drug occurred in from fifteen to twenty-six hours. In a second smaller group of 6 cases the maximum effect occurred in from six to nine hours. The cause of the difference between the two groups is not apparent. In a case of auricular flutter in which the normal cardiac rhythm supervened after digitalis was given no statement as to the maximum effect can be made.

In order to determine the length of time which the drug controlled the heart the patients were kept constantly in bed and the ventricular rates were counted by the stethoscope several times a day. When the ventricular rate began to accelerate and the pulse deficit to increase the drug was considered to have begun to be ineffectual. At this time another dose of digitalis, usually half the amount originally given, was followed by a prompt fall in the ventricular

rate and in the pulse deficit. The rise in the ventricular rate was practically always accompanied by an increase in the symptoms of cardiac inefficiency.

In 12 cases in which the time when the drug began to be ineffectual was clearly indicated, digitalis affected the heart for from four to fifteen days, the effect lasting on an average of nine days and six hours. In 1 case the ventricular rate remained slowed for twenty-two days, when the patient was discharged from the hospital without receiving another dose of the drug, although the primary effect had been very striking. In another case the ventricular rate began to accelerate thirty and twenty-eight hours respectively after each dose of 10 c.c. of the tincture, given several days apart. In the remaining 12 cases no statement regarding the duration of the effect can be made, as subsequent doses of the drug were given before the effect of the initial dose had begin to diminish, or, as in 1 case in this series, the patient died four days after the initial dose.

From this series of cases it may be stated, however, that although the effect of a single large dose of the tincture of digitalis on the heart is not constant, it usually lasts from four to fifteen days, and averages nearly ten days.

The persistence of the action of digitalis is of considerable practical importance, and has been the subject of several investigations. Hatcher[1] has shown that various digitalins vary in their persistence in experimental animals and that the persistence also varies markedly in different animals. He showed that the effects of digitonin and digitalis persist longer than do those of the other digitalins in common use, especially in cats. He found that the effects of a single large dose of these drugs, administered intravenously, may persist for a full month. Cohn, Fraser and Jamison[2] investigated this subject, determining the persistence of the drug administered orally to patients by the change in the T-wave of the electrocardiogram. They found that this change, which was brought about by digitalis, persisted for from five to twenty-two days after the administration of the drug was stopped. Although this method of determining the effect of digitalis was not consistently followed in our series of cases,

[1] The Persistence of Action of the Digitalins, Arch. Int. Med., 1912, x, 268.

[2] The Influence of Digitalis on the T-wave of the Human Electrocardiogram, Jour. Exp. Med., 1915, xxi, 593.

the impression was gained from several cases so studied that the return of the T-wave of the electrocardiogram to the form present before digitalis was given occurred a day or two later than the acceleration of the ventricular rate.

Eggleston[1] has also been among those who have studied the duration of digitalis action in man. He determined the length of time that various cardiac disturbances produced by the drug persisted and found that coupled beats (regularly recurring premature ventricular contractions) persisted for from four to twelve days after digitalis was discontinued, while other disturbances of the cardiac mechanism caused by digitalis persisted for a shorter length of time.

A matter that has been frequently discussed regarding the effect of digitalis when administered by mouth has been the question of the rapidity of its absorption from the alimentary tract. The study of our series of cases seems to throw some light upon this subject. It has been customary to consider the absorption of digitalis from the alimentary canal as irregular, slow and uncertain and the factor of absorption has been called upon to explain differences in the amounts of the drug required to produce the same effects in different individuals. Recently, Wedd[2] found there was a wide difference in the amounts of digitalis necessary to produce certain toxic effects in different individuals, the individual variation being from 20 c.c. to 100 c.c. of the tincture given in large but not single doses. The variation, he believes, is due to variations in absorption. There is, no doubt, definite difference in the rapidity of absorption of different digitalis preparations, as Haskell, McCants and Gardner[3] have shown experimentally, and they find that the tincture is better absorbed from the gastro-intestinal tract than the infusion, and is equally as well absorbed as other preparations.

Eggleston concluded from his study of the effects of large doses of the drugs that digitonin was more completely absorbed than digitalis, but, nevertheless, he found that both of these preparations are probably rapidly and fairly uniformly absorbed from the alimentary canal of man.

[1] Clinical Observations on the Duration of Digitalis Action, Jour. Am. Med. Assn., 1912, lix, 1352.

[2] Observations on the Clinical Pharmacology of Digitalis, Bull. Johns Hopkins Hosp., 1919, xxx, 131.

[3] The Rate of Absorption of Various Digitalis Preparations from the Gastro-intestinal Tract, Arch. Int. Med., 1916, xviii, 235.

The fact that a single large dose of the tincture of digitalis uniformly affected the heart of all of the cases in our series in which its initial effect could be determined in from two to five hours, offers a strong argument for the fairly rapid and uniform rate of absorption from the alimentary tract of patients with heart disease. It is true that the maximum effect did not show so uniform a relation to the time of administration, but it seems probable that factors other than absorption may have been responsible for the variations in the time required for the maximum effect to occur.

It is this rapid and uniform rate of action of the drug when administered in large single doses as herein described, which especially commends the use of digitalis in this manner therapeutically. It is felt that further studies are required before such large doses as were given should be recommended for general use, especially when patients are not under constant observation in hospitals. But the method has been sufficiently tried so that it seems entirely justified whenever rapid digitalis action is strongly indicated, and our experience leads us to believe that it is a much safer method of obtaining rapid digitalis action than the intravenous administration of digitalis bodies, especially strophanthin. Nearly all the cases reported in this series showed very striking clinical improvement within a few hours after the administration of the single large doses of the tincture of digitalis. It is particularly on this account that it is felt that Eggleston's conclusions as to the dosage of the drug are essentially correct.

Summary. A series of 26 cases of auricular fibrillation or flutter are reported, to which large single doses of the tincture of digitalis were administered by mouth. The drug used was standardized and was usually given in doses ranging from 15 c.c. to 25 c.c.

The study of these cases demonstrates that such doses of digitalis affect the heart of cases of auricular fibrillation or flutter at a relatively constant time after administration, in from two to five hours, indicating that the drug is absorbed from the alimentary tract at a fairly rapid and uniform rate. The series of cases also demonstrates that the maximum effect on the heart is usually obtained in about twenty-four hours and generally continues to be effectual for from four to fifteen days, or on an average of nearly ten days.

OBSERVATIONS ON THE EFFORT SYNDROME AMONG THE DRAFTED MEN AT A RECRUIT DEPOT

By LOUIS M. WARFIELD, M.D.
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One of the interesting medical problems which the late World War brought to our attention was that having to do with the detection and disposition of a rather large group of apparently healthy young men who were unable to keep up in the pace set for the recruits. These men did not feel or appear ill. So far as they were aware, they were just as normal as any other men except for the fact that they were totally unable to take part in athletic sports. Finding that they could not engage in violent exercise, they had accepted their limitations and had gravitated to occupations more or less sedentary where they were able to make a living. Some of these men were totally uneducated, others had had the benefits of at least a Grade School education. There was a surprising number of farmer boys from the States of Arkansas and Missouri. The symptoms presented by these men were quite uniform in character. These were on slight exertion: breathlessness, precordial pain, dizziness or actual fainting, palpitation of the heart and a feeling of utter exhaustion. Besides there were cold, clammy, cyanosed hands and feet, a tendency to sweat profusely, often sleeplessness and dull headache. Such sympoms are well known to be present in many recently convalescing from illness and were particularly seen among men who were recovering from streptococcus pneumonia and from empyema.

To the group of subjective symptoms brought out upon slight exertion in apparently normal men, or better in men in whom no organic lesion could be demonstrated, Thomas Lewis gave the name

"effort syndrome." His study was first upon men invalided from the British front. These men had been tagged D. A. H. (disordered action of the heart). The marked psychoneurotic element presented by many of these men so labeled directed attention to a particular organ and seriously interfered with recovery. Later Oppenheimer who was working with Lewis suggested the term neurocirculatory asthenia.

This is essentially the same syndrome so ably described by Da Costa after the Civil War and called by him "irritable heart." There had been hints of this same disorder in the British literature following the Crimean War. The disorder was little known, however, to this generation of medical men. The distinguishing characteristic of the syndrome is that it is brought out on very slight exertion. At rest the pulse may be normal. The blood-pressure is not abnormal.

The syndrome was noticed at first among men invalided from the Allied front who had been gassed, had suffered from shell shock or had broken down under the terrible strain of the campaigns. Later it was found in increasing numbers among the men in training camps, both abroad and in this country, until the problem became a serious one. To the examiners on the Local Boards a man who looked well, in whom no defect could be discovered, who seemingly became exhausted after hopping 100 times on one foot, and who maintained that exercise always exhausted him, was a slacker. He was looked upon with contempt and shipped to some camp. Only very gradually did it filter back from the camps to the local examiners that such men were not slackers. Had the war lasted another year or two, there is no doubt that most of these cases would have been recognized by the Local Examiners. Had the personnel of the fighting forces been confined to volunteers it is probable that the problem would not have been serious. No man who has found out that he cannot take violent exercise volunteers for hard service. So it was because of the Selective Service Law, and because of the lack of comprehension in the part of the general profession of this syndrome that so many men were sent to camps and accepted for service who had the unrecognized irritable heart.

I first came in contact with this syndrome as a member of an

Advisory Board. Later as a Contract Surgeon on a Cardiovascular Board and afterward as Chief of Medical Service at a Base Hospital. I had opportunity to study a considerable number of men presenting the syndrome.

At the Recruit Depot, Jefferson Barracks, Mo., the problem was to sort out all the unfit and return them to their homes. To pass men on to camps who within a few months had to be discharged was not only expensive but wasteful of valuable time. Acting upon the suggestion contained in Lewis' report and specifically urged later in Oppenheimer's paper, we adopted the only rational means to test the capacity of these men for service, that is put them through exercise and observe the effects upon them. In order that no harm might be done to the men suspected of having the effort syndrome, they were gradually led from very simple to more complex and violent exercises under command of a noncommissioned officer who drilled them under our supervision.

Through the hearty coöperation of the surgeon, Lieut.-Col. C. E. Freeman, we were enabled to house the suspects in tents alongside the Base Hospital and to treat them as hospital cases. We were not concerned with the cure of these apparently normal men. We were only concerned with the question of their probable fitness for military service. Men were put through simple setting-up exercises for fifteen minutes daily or twice daily in groups. The response of every man was taken by the drill master or by us at the end of exercise. Within half an hour his pulse and temperature were taken by the nurse on the ward. All men had as a routine regular charts of pulse and temperature every three hours during the day. The exercise was so timed that it came just before one of the three-hourly periods. As the men passed through the examining barracks all cases of tachycardia found by the heart examiner which did not subside within two minutes were referred to the special cardiovascular examiner. If he could not decide definitely whether the man was to be accepted or rejected, he was sent to the probation ward for study.

In order to arrive at some uniformity of history a simple history form was mimeographed and every case was asked the same questions. The most significant points brought to light were: (1) the

influence of heredity, (2) the voluntary change of occupation to a light or sedentary one, (3) the importance of an actual history of precordial pain on slight exertion with dizziness or fainting spells accompanying the pain. This last point we considered of pathognomonic value. In no case was the final diagnosis of effort syndrome or irritable heart made unless there had been a history of precordial pain on slight exertion dating back one or several years. The value of this was further impressed upon us during the demobilization of a group of limited service men. The writer had the opportunity to reëxamine about twenty men upon whom the diagnosis of irritable heart had been made at the time of mobilization by the cardiovascular examiner who was associated with him in the work. These cases had come to the depot during the height of the influenza epidemic when, for obvious reasons, the exercise class work had to be abandoned. Upon reëxamination twelve proved to have normal cardiovascular response. The interesting point was that in no case was there elicited a history of precordial pain. The men were all office clerks who never took any exercise. Upon entering the army they were nervous, unstrung, and some failed to hop the required 100 times. These men were accepted for limited service only. No doubt some of them, if gradually exercised, could have undergone the work of general military service.

Tachycardia was not always present when the man was at rest. However, on the slightest exertion it was evident and persistent. Practically all had cold, moist, cyanosed hands and feet. The vasomotor skin response was slow, the deep reflexes were exaggerated, the pupils dilated, especially after exertion. The blood-pressure was normal. That there is a large psychoneurotic element in the general make-up of these cases seems indubitable, but that it is always present is not in accord with our observations. All presented at least the cardinal symptoms on slight or moderate exertion, of breathlessness, dizziness, palpitation and precordial distress amounting in most cases to actual painful sensations with the feeling of great exhaustion. A number of our cases were so overcome by exercise that they fainted, sweat profusely and spent sleepless nights. The exhaustion at times lasted over twenty-four hours.

Among approximately 35,000 selective service men, both general and limited service, we studied one hundred and forty-two in hospital and exercised them.

DISPOSITION OF CASES AT EXAMINING BARRACKS

Diagnosed hyperthyroidism (rejected)	60 cases	(45.4 per cent.)
Diagnosed pulmonary tuberculosis (rejected)	47 "	(35.6 ")
Diagnosed irritable heart (rejected)	21 "	(15.9 ")
Diagnosed cirrhosis of liver (rejected)	2 "	(1.5 ")
Diagnosed bronchial asthma (rejected)	1 "	(0.7 ")

DISPOSITION OF CASES OBSERVED IN THE HOSPITAL

Considered normal (accepted)	44 cases	(27.8 per cent.)
Diagnosed pulmonary tuberculosis (rejected)	52 "	(39.8 ")
Diagnosed irritable heart (rejected)	21 "	(16.2 ")
Diagnosed hyperthyroidism (rejected)	25 "	(14.5 ")

It must be borne in mind that the cases listed here as hyperthyroidism, pulmonary tuberculosis, represent in no sense the number of men rejected for these diseases. They only represent the men sent, in one case to the cardiovascular examiner on account of tachycardia, and in the other group the cases he referred to hospital for further study because of his inability to make at once a final decision. These cases all presented effort syndrome but were sorted out upon further study into their proper diagnostic class.

Cases of true effort syndrome had to be differentiated from the following conditions:

1. Chronic myocardial degeneration: This as a rule was not difficult. Unless the man had a history of definite symptoms of cardiac decompensation at some time following a severe illness he was not classed as chronic myocardial degeneration. Fifty per cent. of our cases of effort syndrome dated their inability to exercise violently from some acute illness. There had never been any breakdown. They simply could not exercise without becoming exhausted. There never was dyspnea, cyanosis or edema. We found only one such case among all the men which came before us. He had been passed before our advent into camp and was referred later from his command. He was a volunteer.

2. Hyperthyroidism: This differentiation was difficult at times. Some cases of effort syndrome had perceptible goiters and often

some tremor of the extended fingers. My associate and I frequently differed in the opinion as to the presence of lagging lids and ability to converge for near vision. The final criterion was the response to graded exercises. The cases of hyperthyroidism, so-called, had the toxic symptoms and eye signs brought out by exercise. Several cases which were borderline cases were accepted before we had developed our methods and were admitted to the hospital from their commands with evident toxic symptoms. We felt that these cases were potential Graves's disease in whom symptoms and signs were brought out by camp life. It is in such cases that acute Graves's disease is seen. We do not believe that any shock is sufficient to bring on acute Graves's disease in a previously normal person.

3. Other diseases: In such pseudo-effort syndrome cases as chronic malaria, uncinariasis, asthma, etc., the history and examination serve easily for differentiation.

4. Simple excitement tachycardias and soft musculature from lack of exercise: In such cases graded exercises served easily in the separation from cases of true effort syndrome.

5. Incipient pulmonary tuberculosis: We found this group the most difficult one to separate from the group of irritable heart. The histories were often quite similar and the symptoms following exercise were in many cases identical. Careful examination and frequent reëxamination did not always serve to furnish data sufficient for a positive diagnosis for army purposes. It was not possible in every case to have *x*-ray stereoscopic plates of the chest, and, further, it was not always possible to interpret the plates as active lesions. At any rate we were not able always to make the positive differentiation. It was in this class that exercise proved to be so valuable. It was found that of all groups this group responded the poorest to exercise and the subjects invariably had a distinct, though at times slight, rise of temperature following the exercises of even fifteen minutes. Frequently increase in physical signs with the detection of râles accompanied the rise of temperature. In the doubtful cases graded exercises served as the final link in establishing the diagnosis. This febrile response was not noted in any other condition.

A method was thus developed at the recruit depot, Jefferson

Barracks, Mo., which enabled us to sort out the cases of irritable heart before they were sent to training camps. This method was simple, practical, and could have been readily put in operation at any recruit depot or mobilization camp. Fortunately the war ended. We felt that we had kept our share of ineligible men out of service and, had the war lasted another year, we are sure that sorting could have been done so carefully that much valuable time and many hundreds of thousands of dollars could have been saved in the training of these unfit. In no case did we succeed in increasing the capacity of the men with irritable heart for exercise by means of the graded exercises. They were never improved; on the contrary, some appeared to be harmed even by slight exercise. We could not confirm the results of Thomas Lewis and others, who were dealing with men invalided from the front. Approximately 20 per cent. were returned to full duty. Not one of our cases improved under graded exercises. All were unqualifiedly rejected for general military service, a few selected ones with special qualifications were later accepted in the limited service group.

ON THE CLINICAL SIGNIFICANCE OF POSTURAL CHANGES IN THE BLOOD-PRESSURES, AND THE SECONDARY WAVES OF ARTERIAL BLOOD-PRESSURE [1]

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I. The arterial blood-pressure is the direct driving force of the blood: Its maintenance within certain bounds involves the co-ordinated activity of numerous vital functions; its failure to sustain the normal average leads inevitably to general physiological disaster.

Estimations of the blood-pressures under static conditions of the body have a recognized value, but a far greater range of information is conveyed by the reactions of those pressures to strain imposed upon the vascular apparatus.

An extremely simple means of varying the strain upon the cardio-vascular mechanisms is afforded by changing the posture of the body.

When the arterial blood-pressures are measured, first with a subject lying flat upon his back and then standing upon his feet, there is found to be a difference in the quantitative relations of the systolic, diastolic and pulse-pressures which should be ascribed to the hydrostatic pressure of the blood in the upright posture and the opposed physiological compensations which prevent the fluid settling below the heart.

The writer will assume that in the healthy subject a change from the recumbent to the standing posture induces usually no variation

[1] Abstract of a paper which appeared in full in the Am. Jour. Med. Sc., December, 1919, No. 5, clviii, 786.

or a rise in systolic pressure, while the diastolic pressure practically always increases and the pulse-pressure decreases.

It is important to keep in mind the relative physiological significance of these three elements of the blood-pressure. Broadly speaking, with a given pulse-rate, the systolic blood-pressure measures the evolution of energy in the heart. When it is below normal tissue nutrition suffers; when above normal acute or chronic diseases of the arteries may supervene.

The diastolic pressure measures the tonicity of the arterial tree and is an index of vasomotor activity. It is the force which determines the inflow of blood to the coronary system. When in excess, conditions for improvement in cardiac nutrition are realized but, at the same time, the mechanical impediment to outflow of blood from the ventricles increases very fast with dilation of these chambers; diastolic hypertension leads to cardiac dilatation and asystole unless compensated by corresponding vigor of heart-beat. When the diastolic pressure is subnormal, although the lowered resistance favors emptying of the left ventricle, the nutrition of the heart itself is prone to suffer, and fainting or sudden death may be expected to attend such a lowering of the head of pressure as will render it incapable of filling the coronary vessels.

Estimation of the pulse-pressure, or difference between the systolic and diastolic pressures, is of the utmost importance. Physiologists have clearly indicated that the chemical and physical processes of the body demand for their normal development a nutritive stream which is pulsatile in character. Moreover, it has been shown that in the healthy subject, and most probably in the class of cases treated in this paper, the size of the pulse wave, or the magnitude of pulse-pressure, measures the systolic output from the left ventricle. A pulse-pressure less than 30 mm. Hg. is distinctly subnormal and may be taken to signify impaired tissue nutrition and morbid symptoms are especially liable to be referred to the nervous system.

The present study grew out of the consideration of a large number of patients, none of whom showed obvious signs of organic disease but who, despite a great diversity of morbid symptoms, presented the common evidences of general functional insufficiency, such as

undue fatigue with effort, nervous instability, lack of staying power and more or less of the manifestations usually attributed to "neurasthenia." It was found that these persons were almost always the subjects of vascular hypotension, though a record of the blood-pressures taken in the recumbent posture presented nothing distinctly abnormal. On assuming the erect posture, however, a circulatory insufficiency became apparent and increased in gravity the longer the position was maintained. Two classes of circulation disorder could be distinguished: In one there was a fall of systolic pressure of 10 or 15 mm. Hg. in the erect posture, and this frequently became progressive, so that the observation was necessarily interrupted to avoid fainting. The result was evidently an effect of blood ptosis, due chiefly to lack of compensatory vascular constriction in the splanchnic area and to failure of tension in the abdominal wall.

In the second, and more common class of cases there was no marked lowering of systolic pressure in the erect posture but the diastolic pressure rose to an inordinate height, resulting in a corresponding diminution of the pulse-pressure, which might fall as low as 12 or 15 mm. Hg. A combination of these two forms of disorder was frequent; the one common character in each kind of failure was diminution in the pulse-pressure.

An intimate study of these cases of functional insufficiency led to the conclusion that practically all were characterized by some form of toxemia, of which two etiological groups were recognized. In one a so-called focal infection, as manifested in the teeth or tonsils was incriminated.

But a more common source, or at least accompaniment, of the circulation insufficiency in question is believed to be due to a low grade of pulmonary tuberculosis. This indictment is based on the presence of certain morbid auscultatory signs and on the demonstration of organic changes on *x*-ray plates of the lungs. The important conclusion is reached that the universal tuberculous infection is prone to develop into a larval form of pulmonary tuberculosis which remains quiescent without progressing to the "clinical" form of the disease.

Nevertheless, an intoxication arises from the pathologic nidus

and manifests its effects not as disease in the lungs but through its interference with normal metabolism. If the significance of the data leading to this conception of "occult tuberculosis" is sustained by further research there is reason to hope that mastery of the lethal disease will be accelerated by the uncovering of its secret places.

II. A prominent feature of carefully conducted observations on the blood-pressures is the secondary waves, which fall into two groups, one of which is synchronous with respiratory movement and the other has a slower rhythm and possibly represents the vaso-motor waves of Traube. Secondary waves of blood-pressure are more or less common to all subjects but are especially characteristic of functionally subnormal cases such as have been treated in the preceding section, and they are usually more in evidence in the erect than in the recumbent posture.

The author has practically uniformly found that the highest systolic pressure, determined by the auscultatory method, coincides with some part of the phase of expiration, the lowest systolic pressure falls about the peak of inspiration. The two systolic pressures commonly differ by 2 to 5 mm. Hg. but not infrequently the difference amounts to 10 to 15 mm. Hg. with ordinary breathing.

The secondary waves of the remaining class may have the same rhythm as the respiration or one that is of any slower rate; several minutes may elapse between secondary wave crests. The depth of the wave, or distance between crest and trough, is commonly, perhaps, 5 mm. Hg. but may reach a value of 20 mm. Hg. There is reason for believing that predominance of this variety of blood-pressure variation predicates excessive and ill-sustained physiologic effort in the maintenance of the mean arterial pressure; it thus becomes of distinct diagnostic value.

Estimation of the blood-pressure by the auscultatory method is occasionally subject to annoying interference through the elimination of one or more of the sound phases. In normal subjects this is a rare occurrence but in persons of weak circulation, such as are treated in this sketch, it is a very common happening; it is itself a sign of circulation insufficiency.

SOME OBSERVATIONS ON THROMBOSIS OF THE CORONARY ARTERIES

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(ABSTRACT)

THERE were brought out mainly, points regarding the symptomatology and diagnosis. The term "angina pectoris" should, he thought, be eventually dropped, and replaced by the term "cardiac pain." There were many causes of pain in the cardiac area. The main causes on the part of the arterial system were, apart from aneurysm, as follows:

1. Hypertension with or without dilatation of the arch of the aorta, and with or without narrowing of the orifices of the coronary arteries.
2. Diffuse dilatation of the arch of the aorta, so-called Hodgson's disease.
3. Syphilis of the aorta, aortic valves and coronary arteries.
4. Disease of the coronary arteries themselves.

The types of disease usually encountered in the coronary arteries were:

1. Diffuse disease.
2. Narrowing or closure of the orifices.
3. Closure of the lumen by atherosclerosis or by thrombosis.

Syphilis as an etiological factor was mentioned. The other causes would be taken up at another time.

If a large branch of one of the coronary arteries was rapidly closed by a thrombosis, or was slowly closed, and there was interference with the circulation of the heart because of disease in the collaterals, the usual sequence of events was as follows:

1. Closure of the artery.
2. Infarction of the heart muscle.
3. Reactive pericarditis over the area of infarction.
4. A more or less latent period followed by aneurysm of the heart, rupture of the heart, or death from myocardial insufficiency.

This sequence of events had been described by Kernig and Sternberg.

Thrombosis was more apt to be accompanied by gastric symptoms than by other forms of coronary arterial disease. Besides the occurrence of pericarditis, polynuclear leukocytosis was often valuable for diagnosis, because it indicated, in the absence of other causes, infarction of the heart muscle, and that usually meant a coronary closure. When one was in doubt as to whether the symptoms were due to thrombosis, a hint could be obtained by examining the arteries in the lower extremities, and finding closed vessels there.

The last mentioned facts would help in determining whether the patient, who was suffering from a cardiac disturbance with pain, had had a coronary closure before. Another point of value was the history. If the patient gave a history of having had an attack that was diagnosed as "ptomaine poisoning" or "gastritis," and had afterward had to stop walking because of pain in the chest, then it was most likely that the patient had a thrombosis of the coronary artery. Another symptom of value, Dr. Libman stated, was a peculiar color of the face that he had found in a number of cases of old closure of the coronary artery. It was difficult to describe this color; the nearest description of it having been given by Sansom, who did not interpret correctly what it meant: "it was a leaden tint spread over an earthy hue of skin."

Patients suffering from cardiac pain due to diffuse dilatation of the arch of the aorta, also had a rather characteristic waxy paleness of the face. Not all patients, who had an old standing thrombosis of the coronary arteries, developed the typical color, but when it occurred it was almost pathognomonic.

Angina sine delore was believed by the speaker to be a real clinical condition. When thrombosis of a coronary artery occurred in a patient that was not sensitive to pain, pain could be absent. In other words, the so-called angina sine dolore existed because some people are not sensitive to pain.

Three times it had been possible for Dr. Libman to suspect that the right coronary artery was thrombosed rather than the left. An enormous acute enlargement of the liver in a case which was evidently one of thrombosis of a coronary artery, seemed to indicate that the right coronary artery was involved. In one case, by the use of some of the points mentioned, it was possible to suspect that the patient suffered from an old thrombosis of the left coronary artery, and a recent thrombosis of the right coronary artery, the diagnosis being confirmed at the autopsy.

Aneurysm of the heart could be suspected in a patient who was known to have a coronary closure, if at a later period there was found to be a very marked good pulsation of a large area of the left ventricle, with absent or very weak heart sounds.

Dr. Libman finally discussed the question of thrombosis, both of the coronary arteries and the cerebral arteries, pointing out that the tendency to thrombosis was something apart from the tendency to get the arterial disease. Atherosclerosis of the heart and of the brain was very much more frequent than the occurrence of thrombosis in such arteries. It was important, therefore, to discover what caused the tendency to thrombosis in certain individuals, and what could be done to prevent the condition.

CARDIAC DIAGNOSIS IN THE LIGHT OF EXPERIENCES WITH ARMY PHYSICAL EXAMINATIONS

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During the period of nineteen months which elapsed between the entrance of the United States into the war and the signing of the Armistice, approximately 4,000,000 soldiers, most of them recruits, were subjected to a special physical examination of their circulatory apparatus by officers chosen for their supposed special fitness for this work. No similar examinations upon any such gigantic scale have ever before been attempted.

It seems appropriate at this time to attempt to take stock of what has been accomplished by all this elaborate effort; to inquire whether, in the first place, the direct and immediate benefits to the army have been such as to justify this effort; and, in the second place, whether these examinations have added anything of permanent value to our knowledge of cardiac disorders or of cardiac diagnosis.

In the present paper no attempt will be made to answer the first query further than to express the belief that the results of the policy of the Surgeon-General of having the cardiovascular examinations of recruits made only by officers of special training and qualifications have more than justified the added expense in personnel, time and money.

As for the question as to whether anything of permanent value has been added to our knowledge of cardiac disorders and of cardiac diagnosis, that can be answered unhesitatingly in the affirmative. There can be no doubt that a real advance has been made in certain phases of cardiac diagnosis, and it is interesting to note that this

advance was made not through refinements in laboratory technic or by means of more delicate instruments of precision, but chiefly through the opportunity afforded to examine an immense number of young men, almost all of whom were normal subjects, and to learn the frequency and the extent of normal variations of the physical signs of the heart. This extension of our knowledge of the normal variations I should be inclined to place as the most important gain made in cardiac diagnosis. Next to this should be put the gain in knowledge of the functional disorders of the heart, especially of the so-called irritable heart; and, third, I should place the advance in the diagnosis of the milder forms of organic valvular disease.

Three types of cardiac disease, which in civil life are among the commonest seen by the hospital physician, were conspicious by their rarity: (1) as was to be expected, the degenerative conditions common to middle and old age; (2) the severe forms and the advanced stages of rheumatic valvular disease, and (3) syphilitic disease of the aorta and heart. The extreme rarity of syphilitic disease deserves in passing a word of emphasis. Among 1,000,000 examinations of drafted recruits there were 11,562 rejections for cardiovascular disorders. Of this number only 20 were rejected, with the diagnosis of thoracic aneurysm. While this figure doubtless does not represent fully the incidence of the disease, and while an occasional aneurysm manifested itself during military service, they were, nevertheless, extraordinarily rare. Much the same may be said concerning the syphilitic type of aortic insufficiency which all the available evidence shows to have been extremely rare, even among the negro troops. Indeed, when one considers the incidence of syphilis among males between the ages of twenty-one and thirty-five years, one might venture, on the basis of the army examinations, to formulate something approaching the dignity of a law, to the effect that *in cases of acquired syphilis the clinical evidences of involvement of the aorta and heart almost never appear before the thirty-fifth year.*

The examiners, as has been said, were selected for their supposed special fitness for this work, as shown either by their past experience or by their response to the special training furnished them by the

army schools. Although it would be incorrect to say that all of these several hundred special cardiac examiners possessed exceptional qualifications for the work in hand, it is unquestionable that many of them did. In making up the various groups of examiners, pains were taken to see that in each group at least the officer in charge should be known to be a clinician of experience and special training. Moreover, with the records at hand from the examining boards of each of the fifty or more camps and recruiting stations it was possible to establish averages and controls by which to assess the diagnostic accuracy of the individual boards. Supervision and control were further exercised by occasional visits of inspectors and consultants. In these various ways it was possible, therefore, to keep in touch with the work done in the different camps and to ascertain the difficulties and common errors in diagnosis. Methods of examination and criteria of diagnosis were standardized, insofar as possible, by rules prescribed by the Surgeon-General and issued first in the form of a circular of instructions. These instructions were drafted with consummate skill by the late Major T. C. Janeway, and have formed the basis for all the later rules governing such examinations included in the selective service regulations.

Normal Variations of Physical Signs. As has been said a realization of the fact that the physical signs of the normal heart are subject to much more frequent and much wider variations than has generally been supposed is to be regarded as one of the important gains for cardiac diagnosis which has come out of the war experiences. These variations affect every type of cardiac physical sign; the position of the apex-beat, as shown by inspection and palpation, the distinctness and character of the cardiac impulse, the area of cardiac dulness, the character and intensity of the heart sounds, all are subject to surprisingly wide variations in perfectly normal individuals. Only a few of the more important of these variations can be discussed here.

The distinctness and the character of the cardiac impulse depend to a very marked degree upon the special conformation of the thorax. If the latter is deep and roomy only a faint and sharply localized apex-beat will be seen and felt. If, however, as often happens, the chest is flat and the space between the bodies of the

vertebræ and the sternum very small the heart gives the impression of being flattened up against the chest wall, and there is a marked visible and palpable impulse which may involve all the precordium to the left of the sternum and occasionally even the sternum itself. This together with the associated large area of dulness may readily be misinterpreted as indicating the existence of some cardiac enlargement.

The character and intensity of the heart sounds vary greatly in different individuals under similar conditions and in the same individual under different conditions. Rest, exercise, excitement and change of posture all have their effect in modifying the character of the first heart sound and in changing the intensity of both sounds.

Accidental Murmurs. In the modification of the first heart sound the point at which such a changed sound deserves to be called a murmur is one concerning which disagreement is common, but even under the most rigid interpretation of the term the occurrence of such systolic accidental or functional murmurs is surprisingly frequent. When the murmur is located over the base of the heart its true nature is much more likely to be recognized than when it is apical, and yet such apical accidental murmurs are very common. It is not possible to give accurate statistics, but I am convinced, in the light of my own experience, that it would be conservative to say that at least nine-tenths of all apical systolic murmurs in young adults belong to the class of accidental or functional murmurs. Rothschild's figures, which bear upon this point, will be quoted in discussing mitral insufficiency.

These apical systolic accidental murmurs have several features by which they can usually be recognized. First and foremost is their inconstancy. They may be absent during rest and be pronounced after exercise or during excitement. The first sound may be quite clear and normal in the erect posture and have all the characteristics of a murmur in the recumbent position; in the second place they usually show no tendency to be transmitted to the left of the apex; then, too, the murmur is obviously only the modified and changed first sound; it is not something clearly distinct from and additional to the heart sound as is so commonly the

case with the murmur of mitral insufficiency. Lastly, such accidental murmurs seem rarely if ever to have the peculiar high-pitched, whizzing or blowing quality usually possessed by those due to mitral insufficiency.

The basal systolic accidental murmurs have much the same characteristics as those at the apex. When heard only to the left of the sternum they are usually readily recognized; but when, as occasionally happens, they are audible over both the pulmonic and the aortic areas, they may be mistaken for the murmur of aortic stenosis.

Diastolic Accidental Murmurs. The teaching that accidental murmurs are always systolic in time is in general sound, even although the statement is not strictly true. Exceptions to that rule do occur, but they are certainly rare. I have myself seen three undoubted instances of diastolic cardiorespiratory murmurs heard over the base of the heart and bearing a very close resemblance to the murmur of aortic insufficiency. Two of these cases were young officers in whom the murmur had been accidentally discovered, and who after examination by a board had promptly been recommended for discharge because of aortic insufficiency.

The Irritable Heart of Soldiers. (*The Effort Syndrome, Neurocirculatory Asthenia.*) Notwithstanding the fact that for nearly fifty years almost every text-book of medicine has contained some account of the condition described by Da Costa as "the irritable heart of soldiers," it is nevertheless true that up to the beginning of the war a practical knowledge of that disorder was entirely lacking. It is doubtful if one physician in a thousand had ever ventured to make the diagnosis or had any confidence in his ability to recognize a case if he should see it. It was generally looked upon as an affection peculiar to war conditions and without its counterpart in peace times.

From the very first day of the army heart examinations, however, this neurosis obtruded itself upon the consciousness of the examiners in no uncertain manner. It was far away the commonest disorder encountered and transcended in interest and importance all the other heart affections combined.

One of the most surprising things about the "soldier's heart"

was the discovery that in a majority of the cases the symptoms of the disorder were not first manifested under the strain and stress of war but had existed in the recruit for years, often for many years, before the onset of his army career. These cases made up the so-called constitutional type of the disorder.

In another large group of cases the symptoms appeared in previously healthy men after an attack of acute illness, such as pneumonia, dysentery, rheumatic fever or influenza. In most of these "post-infectious" cases there is no reason to suppose that the fact that the patients were soldiers bore any direct relation to the development of the neurosis.

It is clear, therefore, that the affection is far from being peculiar to the conditions of war or to army life. Only a small proportion of the cases have their origin in such special conditions. Obviously, then, the syndrome must exist and must be of fairly frequent occurrence in peace times, notwithstanding the fact that heretofore we have failed so completely to recognize it. With the knowledge of the disorder gained in the war, however, there should be no question of its proper recognition in the future, and the dissemination of this knowledge throughout the profession will constitute one of the most important of the war's contributions to cardiac diagnosis.

All the experience of the army heart examinations has shown the great danger, even with experienced examiners, of mistaking this neurosis for some organic disease of the heart, in contrast to the very rare error of mistaking such organic diseases for the effort syndrome. The "soldiers' hearts" were very apt to be diagnosticated either as myocarditis or as mitral insufficiency or mitral stenosis. It was indeed often difficult to believe that a soldier who, on even moderate exertion, showed such an array of striking symptoms (dyspnea, exhaustion, precordial pain, tremulousness, cyanosis, extreme tachycardia) could be suffering merely from a neurosis. Moreover, certain of the physical signs sometimes bore a close resemblance to those of mitral insufficiency and mitral stenosis. The pronounced and widespread cardiac impulse often suggested cardiac enlargement; the first sound at the apex was usually extremely short and sharp and the second pulmonic sound often

very loud; a systolic accidental murmur was sometimes present and the suggestion of a thrill was often given to the palpating hand in the apical region. Because of the rapid heart-rate it was sometimes easy to persuade one's self, erroneously, that this slight thrill was presystolic in time. Thus with such a combination of pronounced symptoms and suggestive physical signs it is not surprising that a good deal of time was needed to educate the great body of medical officers to the true nature of these cases.

Diagnosis of the Mild Forms of Valvular Disease. The progress made during the war in the diagnosis of valvular disease has been chiefly in the direction of recognizing the need for much greater caution in making such diagnoses than was formerly generally believed to be necessary or proper. The recognition of the great frequency of normal variations from the conventional physical signs, including the prevalence of systolic accidental murmurs, as well as the knowledge gained concerning the effort syndrome and the readiness with which it may be mistaken for valvular disease, has led to the conviction that in the past this latter diagnosis was made much more frequently than it deserved to be.

The instances of valvular disease encountered in the army examinations were, practically all of them, of mild type—all the more severe and obvious cases had been eliminated by the examinations of the local draft boards—and it was characteristic of these mild forms of valvular disease that symptoms, as distinguished from physical signs, were entirely lacking. These men, almost without exception, gave a normal cardiac response to exercise, showed the same degree of physical strength and endurance as normal men and could be distinguished from these only by the physical signs of the heart.

It remained throughout the war an amazing paradox that a disorder in which the heart was known to be intrinsically normal should give rise to such pronounced cardiac symptoms, whereas the cases of valvular heart disease were so completely free from symptoms.

Concerning the diagnosis of lesions of the aortic valve there is little to say. These lesions were rare and were usually correctly diagnosticated. Not more than one recruit in every thousand was

rejected for disease of the aortic valves, although every such case discovered was rejected. Aortic insufficiency was the one valvular lesion in which the tendency to err was in the direction of making the diagnosis too infrequently. When the diastolic murmur was faint and high pitched it was occasionally overlooked, and this error was, I think, due chiefly to the failure on the part of some examiners to realize that this particular murmur is often better recognized with the naked ear in contact with the chest than through the medium of the stethoscope.

With respect to mitral lesions the examinations demonstrated clearly that the correct diagnosis of the mild forms of these two valvular lesions is by no means always as simple and easy as we have been accustomed to think. They showed, further, that when mistakes in diagnosis are made they are almost invariably in the direction of finding some valvular damage when it does not exist rather than in overlooking a lesion when it is present.

Mitral Insufficiency. The effort syndrome was the condition most frequently mistaken for mitral insufficiency, as indeed it was also for mitral stenosis. The rapid and violent heart action and pronounced cardiac impulse frequently gave the impression of cardiac hypertrophy; if, in addition, there was to be heard an apical accidental murmur the resemblance to mitral insufficiency might be close and, to the uninitiated, the diagnosis would seem to be confirmed by the pronounced subjective symptoms of precordial pain, dyspnea, palpitation, etc. With increasing experience in the recognition of the effort syndrome its confusion with mitral insufficiency became less and less frequent, for the two conditions bear little real resemblance to each other. The tachycardia, which is so constant and marked a feature of the "soldiers' heart," is no part of the clinical picture of mitral leakage, and, as has been said, the pronounced subjective symptoms were characteristic of the neurosis and were altogether lacking in the valvular cases.

The question has been much discussed of late as to whether one is ever justified in making a positive diagnosis of mitral insufficiency on the existence of an apical murmur alone, and in the absence of signs of hypertrophy and of a history of definite attacks of rheumatic fever, even though the murmur have those special characteristics

of transmission and quality which are supposed to belong to that disease. My own attitude toward this question has been modified a good deal by my army experiences and without venturing to be dogmatic upon the subject I am inclined to believe that one will make fewest mistakes in the diagnosis of mitral regurgitation by adhering to the rule of never venturing a diagnosis on the presence of a murmur alone, no matter how characteristic it may seem to be. It is certain that if this rule were generally followed uncomplicated mitral insufficiency would take its place among the less frequent forms of valvular disease, as I believe it deserves to do. In this connection the statistics of Rothschild[1] are very instructive. Assuming the chief criteria for the diagnosis of mitral regurgitation to be (1) cardiac hypertrophy, (2) an apical systolic murmur and (3) a definite history of rheumatic fever, and arguing that the presence together of (1) and (2), or of (2) and (3), should at least raise a grave suspicion of valvular disease, he analyzes the records of the examinations of 10,000 recruits, accepted for limited service, with these points in mind. Among this number there were 870 cases with recorded systolic murmurs, of which only 33, or 3.8 per cent. fulfilled the above requirements for the diagnosis of mitral insufficiency.

Mitral Stenosis. The physical signs of mitral stenosis are usually so distinctive and striking that it may be hard to understand why much difficulty in its diagnosis should have occurred. As a matter of fact, however, there was constantly a tendency to mistake cases of "soldiers' heart" for this form of valvular disease. This tendency was much more pronounced at first than later on, but even when the clinical picture of the effort syndrome had become a familiar and well understood one there were still occasional cases in which the differential diagnosis between this neurosis and mitral stenosis was very difficult. In the former condition the heartbeats are not only very rapid but are usually quick and forcible in character; the apical impulse often is sharp and tapping, the first sound short and sharp and occasionally a suggestion of a thrill may be felt which, because of the rapid heart rate, it is difficult to time accurately. All these signs bear resemblance to those of mitral

[1] Jour. Am. Med. Assn., February 1, 1919, lxxii, 327.

stenosis. Occasionally, too, the first sound is impure or reduplicated, and it is easy to fancy that this is really a very short presystolic murmur.

These physical signs are often very much like those of the heart in exophthalmic goiter, which, as is well known, may closely simulate the signs of mitral stenosis. There are, however, certain differential points which will usually suffice to clear up the uncertainty between the effort syndrome and mitral stenosis. In the first place a rapid heart rate *during rest* is very exceptional in the mild forms of mitral stenosis under consideration. Usually the rate is quite normal, although it may become rapid upon even slight exertion or under excitement. On the other hand anything approaching a normal heart-rate, even during rest, is very unusual in the "soldier's heart."

In the next place a distinct and unmistakable presystolic murmur is so constant a sign of these mild cases of stenosis that this diagnosis is not justified, I think, unless the murmur is heard. It may be audible only in certain postures or only after some exertion, but is rarely, if ever, lacking entirely. No matter how suggestive the other physical signs may be, the diagnosis, in my judgment, cannot safely be made in the absence of an unmistakable presystolic murmur.[1]

Finally, in the mild grades of valvular disease there are lacking all the pronounced symptoms of dyspnea on exertion, faintness, precordial pain, palpitation, tremulousness, cyanosis and sweating, which are such a characteristic part of the clinical picture of the effort syndrome. Two procedures have been suggested recently as aids in clearing up the diagnosis in doubtful cases of mitral stenosis. Morison[2] has found that the inhalation of nitrite of amyl will sometimes cause a doubtful murmur either to become more distinct or to disappear. Rothschild[3] has sought to bring out the murmur in doubtful cases with very rapid heart action by slowing the heart by the use of ocular pupillary pressure.

Summary. The examination of the cardiovascular apparatus of immense numbers of soldiers by specially qualified medical

[1] This view accords with that expressed by Lewis in his recent admirable monograph on the Soldier's Heart.

[2] British Med. Jour., April 20, 1918, i, 452.

[3] Jour. Am. Med. Assn., March, 1919, lxxii, 652.

officers has resulted in a distinct gain to our knowledge of certain phases of cardiac diagnosis. This gain has been chiefly in three directions: A better appreciation of the extent and the frequency of normal variations from the conventional physical signs of the heart; the recognition of the importance and frequency of the syndrome known as the irritable heart of soldiers or the effort syndrome, and an increased accuracy in the diagnosis of the mild forms of valvular disease, especially of mitral insufficiency and mitral stenosis.

Variations from the conventional physical signs of the heart are extremely common in normal individuals and affect every type of physical sign. Of these the systolic accidental or functional murmurs heard at the apex and in the pulmonic area are the most important and the most likely to lead to errors in diagnosis. It is believed that fully nine-tenths of all apical systolic murmurs belong to this class of accidental or functional murmurs.

The neurosis known as the irritable heart of soldiers has been the most frequent, and much the most important heart disorder encountered during the war. Because of the pronounced cardiac symptoms associated with it and the suggestive physical signs it is very likely to be mistaken for some organic disease of the heart, especially for mitral insufficiency or mitral stenosis. The knowledge gained of this disorder during the war indicates that only a minority of the cases have their origin in conditions peculiar to war and that the condition must have existed, and been far from rare, in civil life in spite of our failure to recognize it.

The army examinations have demonstrated that the mild grades of valvular disease, which were almost the only types encountered, show a cardiac reserve power well within normal limits and are remarkably free from subjective symptoms. In this respect they offer a striking contrast to the effort syndrome in which such symptoms are usually pronounced.

The inclination to diagnosticate mitral leakage upon the presence of an apical systolic murmur alone is to be resisted. In the absence of evidences of cardiac hypertrophy or of a history of definite attacks of rheumatic fever it is doubtful if one is justified in making the diagnosis even though the murmur have those features of trans-

mission and quality which are supposed to be characteristic of that disease.

In view of the danger of mistaking cases of soldiers' heart for those of mitral stenosis the latter diagnosis should not be made unless an unmistakable and characteristic presystolic murmur be present.

The extraordinary rarity of cases of syphilitic disease of the aorta and heart among the men examined seems to indicate that the clinical manifestations of syphilis in the aorta and heart almost never appear before the thirty-fifth year.

DISCUSSION

Dr. S. Solis Cohen said that one naturally hesitates to differ with observations so ably made upon a basis of so great experience, yet one conclusion of the speaker seems hardly justified. Mitral stenosis is, if not the most common, at least one of the commonest of organic heart lesions. True, it is one of those said to be "outgrown." Symptoms manifested in childhood may disappear—especially under good hygienic management—toward adolescence, and the patients may live for years without consciousness of trouble. But some cases do show persistent symptoms and manifestations other than murmur. It was his good fortune to have been instructed in cardiac diagnosis by Da Costa, and therefore to have been unable to remain ignorant of the irritable heart of young soldiers, even though he may have failed always to apply the knowledge. Da Costa's pupils ought not—at least—to mistake irritable heart for stenosis. He has believed—and practiced in that belief—that a certain distinct semeiologic physiognomy—found most frequently with presystolic murmurs, it is true—may also, without the murmur, be interpreted as indicating some degree of obstruction at the left auriculoventricular orifice. This does not refer to the period of auricular fibrillation or to the period of auricular weakness that precedes fibrillation or even flutter. But before this, in a certain number of cases the murmur may be absent or inconstant, and yet the conjunction and persistence of certain signs, even with the patient at rest, justifies the diagnosis. The sharpness of the shortened first sound—so that it is often mistaken by inexperienced examiners for the second sound; the jerky action of the ventricle, which knocks up against the chest wall, stops abruptly, falls away, pauses appreciably, and then knocks again—and the great disproportion between this violent, somewhat spasmodic, effort and the small volume and force of the hurried pulse, make up a picture that—especially if there is a history of blood-spitting—has

seemed unmistakable. If signs like these are brought out only upon effort, and are unaccompanied by murmur, that is, of course, a different story. It is their persistence in some degree, under varied conditions, over long periods, and even in the absence of dyspnea and other symptoms of decompensation, that gives them significance.

THE PHYSICAL SIGNS OF FOREIGN BODIES IN THE BRONCHI.

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Through the kindness of my colleague, Professor Chevalier Jackson, an opportunity has been given to study the physical signs in a considerable number of patients with foreign bodies in the bronchi. This study is a discussion of the clinical aspect of some of the problems presented. No attempt is made to discuss the other phases. Dr. Jackson has done this in various publications, and a summary of many of the points can be found in a recent article.[1]

The study of these cases suggests a number of clinical problems: (1) How frequent is the occurrence of foreign bodies in the bronchi? (2) What symptoms and signs are there which are diagnostic or suggestive of their presence? (3) Is there any clinical picture or are there physical signs suggestive of the presence of a foreign body in the absence of roentgen-ray findings? (4) Are there definite physical signs suggestive of a particular kind of foreign body? (5) To what extent can we reduce the chance of error in failing to recognize the presence of a foreign body in a bronchus?

It is evident that we have to discuss very different sets of conditions, and that no one description can cover all the cases. Thus we have certain signs due to the foreign body and the local reaction set up by it, and others due to changes in the lung supplied by that bronchus. The character of the foreign body is important; a safety-pin may do little damage while a peanut causes marked changes very rapidly. One foreign body plugs a bronchus completely,

[1] Jackson, Chevalier: Observations on the Pathology of Foreign Bodies in the Air and Food Passages, Surg., Gynec. and Obst., 1919, p. 201.

another acts as a ball valve. Pus forms below the foreign body and may be retained or escape. The secretions may be forced into bronchi other than the one involved, or from the affected lung into the bronchi of the opposite one, so that signs are found on both sides. The signs may change greatly from hour to hour in acute cases, so that any set description fitting all cases is out of the question.

1. The Frequency of Foreign Bodies in the Bronchi. It is quite impossible to give any statement on this point. In the Jefferson Hospital material they are comparatively common, but this is exceptional, as the patients come from all parts of the United States and Canada to consult Dr. Jackson. Two things suggest that such cases are more common than we have generally supposed. One is the number of patients who come with a history which shows that for months or years a foreign body has been present and unsuspected and the other is the number of patients from the near neighborhood with a foreign body, but without suspicion of it on their part. The roentgen rays have aided greatly in the recognition of certain foreign bodies, but there are substances which do not show in a roentgen-ray plate, and it is for the recognition of these that a study of the physical signs is particularly important. Certainly, the impression has been strongly forced upon me that the condition is much more common than the majority of us have suspected and my memory brings up cases seen in the past in which the presence of a foreign body was probably overlooked.

One point deserves emphasis in this connection—the history. Most of us would suppose that there would be small chance of a foreign body passing into the trachea and then to a bronchus without marked acute symptoms which could not fail to be noticed. We must realize that this is not necessarily the case and that fairly large bodies may reach the bronchi without any acute symptoms. For example, in one case (No. 611[1]) there was no definite history as to when the foreign body, which was an atomizer tip, had been aspirated. The patient knew nothing of it, but on searching his memory remembered that about eighteen months before a tip had disappeared. This particular patient had been thought to have

[1] The numbers are those in Dr. Jackson's series, and are given to identify the cases when reported elsewhere.

tuberculosis. At the time of writing this paper a boy of eight years of age is under observation. He was sent to the clinic for some laryngeal condition and examination shows part of a collar-button in a bronchus. No history can be obtained of any acute onset and there is no clue as to the time of aspiration. Such cases emphasize the need of caution in concluding that the introduction of a foreign body must cause some symptoms or disturbance which can be noted. This point cannot be too strongly emphasized.

My impression is that these unrecognized cases of foreign bodies in the bronchi are by no means rare. Naturally the greatest difficulty arises in the instances in which the body cannot be recognized by the roentgen rays, probably in from 10 to 15 per cent. of all cases. There are two sharply defined groups of unrecognized cases. The first is that in which the body sets up a very acute inflammatory process and death follows in a short time—the diagnosis of pneumonia usually being made. This is particularly likely to follow the aspiration of some variety of nut, especially a peanut, by a young child, and how many of these cases occur we have no means of knowing. The younger the patient the more acute this process usually is and in such cases it is evident that the history is often not complete. The other group is that in which marked changes are set up and the symptoms become chronic, a diagnosis of pulmonary tuberculosis or bronchiectasis being made. In such a case in an adult seen some years ago there were marked signs over the lower right lobe. We suspected the possibility of a foreign body but there was no history to suggest it and repeated roentgen-ray examinations did not aid. After eighteen months of illness she coughed up a small piece of bone. This was followed by rapid recovery.

2. Clinical Features Caused by Foreign Bodies. The greatest possible diversity occurs, as the signs vary markedly. A safety-pin, particularly if closed, is not likely to cause much change in a short time, while a screw or tack which plugs a bronchus results in rapid changes. One substance may plug a bronchus or set up inflammation which does the same thing, and another may entirely plug a bronchus at one time and a little later allow air to enter past it, so that it is evidently impossible to give an exact account of

the signs. The foreign body is more often on the right side and has a tendency to go to the bronchi supplying the lower lobes.

The change in the signs in a short interval is a striking point. In some cases this is apparently due to a change in position of the foreign body, in others air may enter at one time and not at another. Thus in one patient the signs suggested collapse of the involved lobe and a few hours later it was apparently overdistended, suggesting a valve action of the foreign body. The amount of secretion and the effect of coughing on its expulsion may cause rapid changes in the signs. The signs may be local or general; it is not uncommon to find signs over both lungs. Emphasis should be placed on this point, as in some cases the signs are more diffuse on the unaffected side. This may lead to serious error and appears most likely to occur in the younger patients.

There is only one sign which has been present in every patient seen by me, and that is *decreased expansion* of the affected side. It may be the only sign present, as in the following case:

> No. 697. The patient was a woman, aged thirty-two years, who, two weeks before, coughed while holding a safety-pin in the mouth and aspirated it. She felt some soreness in the throat, followed by a tickling sensation and a hacking cough. Two days later she had more severe coughing, followed by pain in the upper right chest. On admission she complained of slight cough and pain in the *right side* of the chest. On examination there was *only one sign* to be found—diminished expansion of the *left* side. The percussion note and the breath sounds were clear. No rales were heard. In view of this the opinion was given that the foreign body was on the left side, but that there was no clue to its position beyond that. The roentgen ray showed an open safety-pin in the left bronchus without any evidence of a pathological process in the lung beyond the pin. Dr. Jackson removed the pin and three hours afterward the expansion was absolutely equal on the two sides.

In some cases it has been possible to hear rales, which may be described as rather characteristic, over a small area. In each case in which they have been observed the foreign body was metallic, but the cases are too few to draw any positive conclusions. These particular rales may be described as very fine and softer than the

early crackling rales heard in lobar pneumonia. They may be compared to the crackle made by very fine tissue paper. In the two

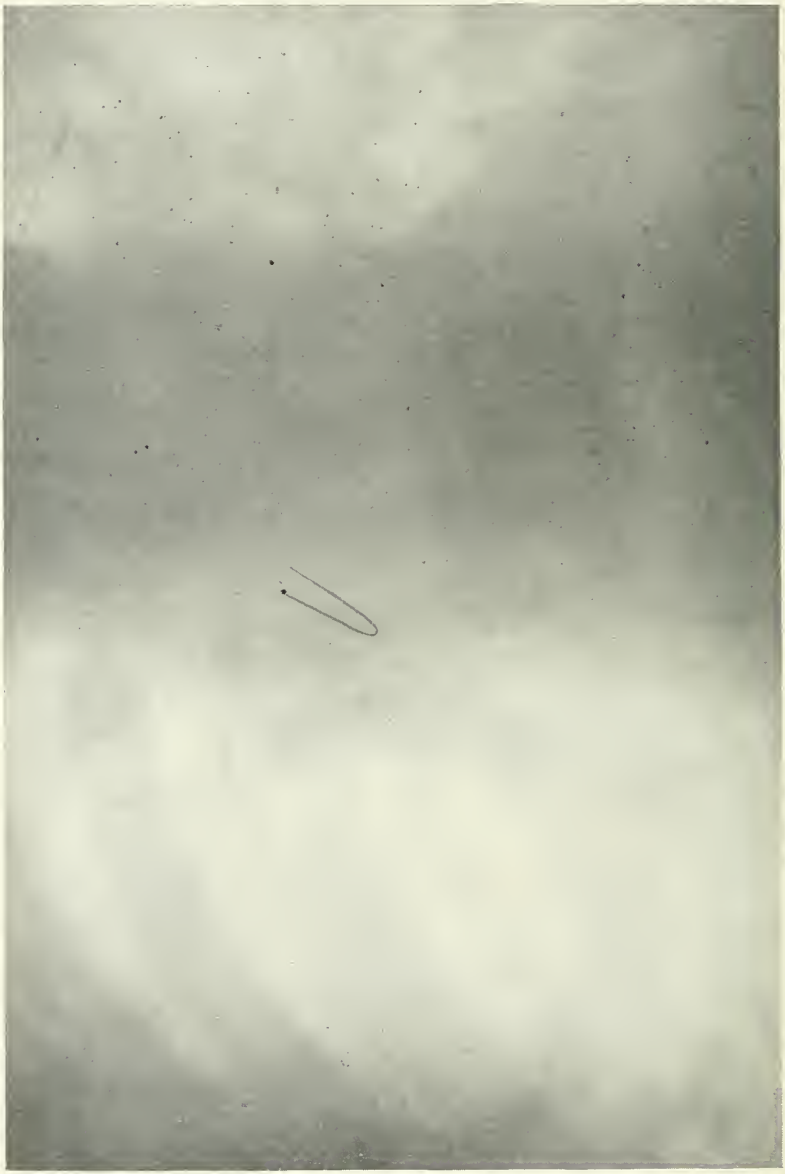

FIG. 1.—Case 690. Staple in right lower lobe of bronchus. Little change below the foreign body.

cases given there was no other evidence of any change in the lung tissue made out by physical or roentgen-ray examination.

No. 683. The patient was a girl, aged eighteen years, who was having some dental work done on December 23, 1918. A dental root-canal reamer was placed in the tooth and the dentist turned to get another instrument. The patient felt the reamer slip out of the tooth and lodge on the tongue. She tried to take hold of it, but it disappeared. She had a paroxysmal attack of coughing but did not feel any sensation of a foreign body in the throat or air passages. Two days later she took ill with what was regarded as an attack of influenza, with which she had a severe cough and considerable sputum. After this she was very weak and had some cough, which was slightly productive. She complained of an occasional sharp shooting pain in the lower left thorax, which seemed to be brought on by coughing. On admission on January 31, 1919, examination showed slightly less expansion of the lower left thorax. The percussion note seemed equal on the two sides. The breath sounds were very feeble on both sides, and this seemed to be rather more marked over the lower left lobe. In the lower left axilla there were very fine crackling rales, which seemed to come from a distance. They were heard mostly at the end of inspiration and were slightly more marked on deep breathing, but were never loud. There were no definite signs of any solidification in the lung tissue. The roentgen-ray study showed the foreign body in the left lower lobe bronchus. There was no evidence of change in the lung beyond it. The reamer was removed on February 1. Dr. Jackson found the trachea very red and inflamed. The left bronchus showed a high degree of inflammation, with adherent masses of thick secretion which surrounded the foreign body, part of which was in the posterior branch of the left inferior lobe bronchus.

It is certainly surprising that there were not more signs with this degree of change in the bronchus. Two days later there was still slightly less expansion of the lower left side and a very few of the fine, crackling rales could be heard on deep breathing.

No. 690. The patient, a man, aged fifty-six years, was seen on March 15, 1919. On March 7, while standing on a ladder holding a staple in his mouth, he endeavored to answer a question and aspirated the staple. He did not have any

symptoms at the time. The next day he complained of tickling in the throat, and a roentgen-ray examination was made which

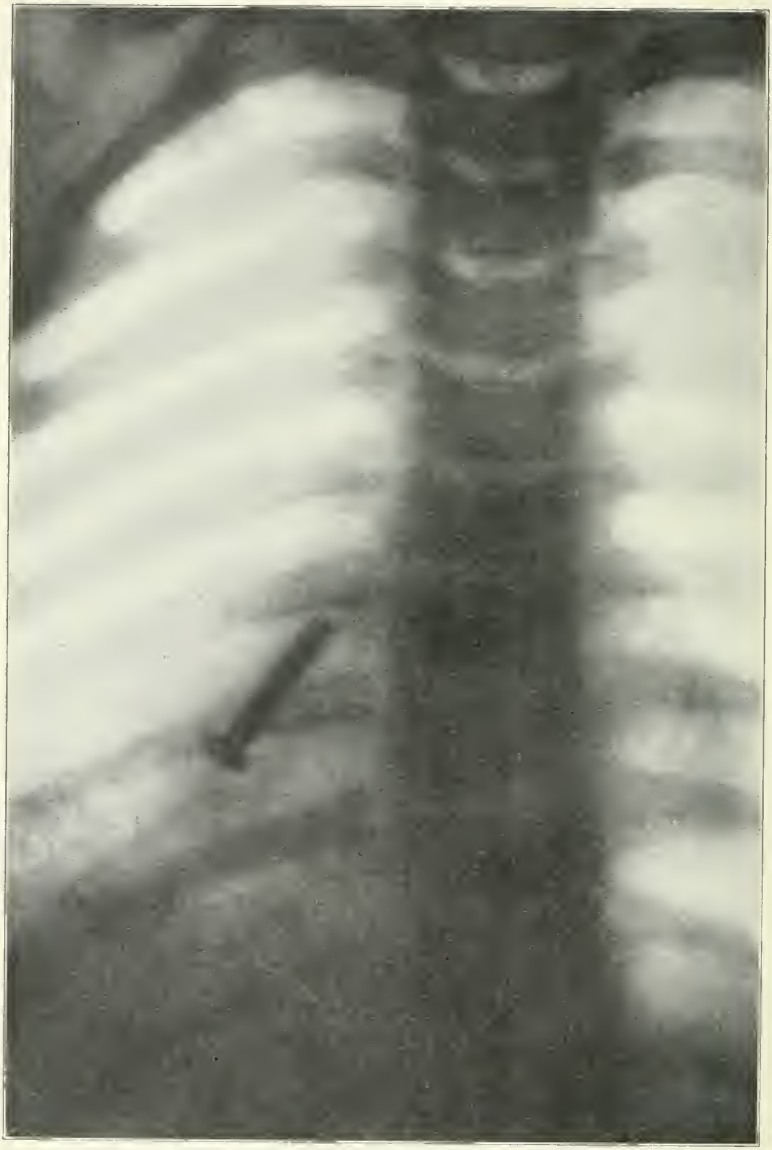

FIG. 2.—Case 684. Foreign bodies in bronchi.

showed the staple in a bronchus. An attempt at removal was made (in another place), but was not successful. At the time of examination the patient stated that the roentgen ray showed the staple in the *left* lung and pointed to the third left interspace as the spot where he felt it. The importance of not accepting a patient's statement as accurate was shown by the examination. This was complicated by the fact that he evidently had old trouble on the right side, and he stated that he was thought to have had tuberculosis in youth. The right shoulder was lower, there was less expansion, the right scapula was longer and moved less, and there was dulness, with harsh breath sounds at the right apex. The percussion note was equal in the two axillæ, but in the lower right axilla there were fine rales at the end of inspiration heard over a small area. These seemed to come from a distance and were extremely fine. They were the same as those heard in case No. 683. No rales were heard on the left side. Despite the positive statement by the patient that previous roentgen-ray studies had shown the staple in the left lung and that he could feel it there, these rales suggested that it was in the right lower lobe bronchus. The roentgen-ray study (Dr. Manges) showed a metal staple in the main bronchus of the lower right lobe and very little pathology in the lung below the staple. Dr. Jackson found the staple in this situation and removed it. The fine crackles were heard unchanged three hours after the removal, but had disappeared the following day.

One hesitates to give too much importance to these rales, but they are different from rales which I have heard in any other condition, and have only been heard in cases in which the foreign body was metallic in character. They are certainly worth keeping in mind, but it is well to state that very careful listening is required to hear them. They might easily be missed in a hurried or perfunctory examination.

The next stage of the development of the signs is found when changes have occurred in the lung. An example is as follows:

No. 684. This patient was a boy, aged three years, seen on January 31, 1919. The history was that on December 21, 1918, it was noticed that the patient had something in his mouth which was suddenly aspirated. A severe coughing attack followed and the patient was blue for a time. In the next two

or three days repeated coughing attacks occurred and there was a slight elevation of temperature. The patient was attended by a physician who made a diagnosis of influenza and later of pneumonia on the left side. During this time the patient seemed to be very ill and had fever, which occasionally reached 104°, with very severe cough and considerable pain in the left side of the chest. Examination was difficult, as the child was crying constantly and was very restless. The expansion was diminished on the right side. The percussion note was clear and hyperresonant on the left side, but on the right side there was some impairment on percussion throughout, slight in the upper part and most marked in the lower right front, axilla and back. The breath sounds were clear throughout the left side and not a single rale was heard. On the right side, on quiet breathing, expiration was not heard, but was distinctly audible when forcible expiration was made. In general the breath sounds were distant over the right side. In the upper part of the right chest the breath sounds were rather higher pitched than normal, but were not tubular. There were many coarse, crackling rales in the lower right interscapular region and a certain number in the lower axilla. After forcible coughing the rales changed somewhat, becoming rather fewer. There was no wheeze heard. The signs suggested that the foreign body was in the lower right bronchus. Dr. Jackson removed a machine screw from the right inferior lobe bronchus. Large amounts of pus escaped during the operation and were coughed up subsequently.

It is interesting to note how frequently the diagnosis of pneumonia is made in these cases. This comes out very frequently in the histories, but a careful study of the physical signs should prevent this error. Fever is very common after the aspiration of a foreign body, and if there is dyspnea, with cough and bloody or blood-streaked sputum, the diagnosis of pneumonia is suggested before the examination of the thorax is made. Decreased expansion on one side and dulness may suggest the diagnosis, but a careful study of vocal fremitus and the auscultatory signs should show that if the condition is pneumonia there is plugging of the bronchus—a rare condition. The writer has not seen pneumonia associated with any case of foreign body in a bronchus. The local signs are usually those due to the supplying bronchus being obstructed. Variations

depend on the quantity of air in the portion of lung, the amount of secretion and the persistence and completeness of the plugging of the bronchus. In many cases there are no breath sounds or rales heard over the affected parts, in others there may be rales but no breath sounds. In the majority the affected portion of lung seems to be airless and in the roentgen-ray plates at early stages shows as a homogeneous shadow. Later fibrosis, abscess formation and bronchiectasis may be found. These show no special peculiarity in the physical signs, but are important in that they may be wrongly diagnosed as tuberculosis.

"Asthmatoid Wheeze." This term has been employed by Chevalier Jackson to describe a sign which is present in a considerable number of cases of foreign body in the trachea or bronchi. He has discussed it in considerable detail in a recent article.[1] This sound can be heard by placing the ear or the bell of the stethoscope close to the patient's mouth. It may be heard with both inspiration or expiration, but sometimes is only audible at the end of forced expiration. Forcible respiratory effort usually increases the loudness and intensity. It differs from the wheezing sounds heard with bronchial asthma, but this difference is difficult to describe in words. The "wheeze" varies in pitch and loudness, depending on the character of the foreign body causing it. In no case in which the writer observed it could the sound be heard over the chest wall. In some cases the sound comes and goes without any explanation being evident. The report of a case in which it was very marked is as follows:

> No. 675. The patient, a white male, aged forty-four years, was admitted on December 20, 1918, complaining of cough and shortness of breath. Four days before admission a dentist was fitting a gold bridge, when it slipped back in the mouth and was aspirated. Following this there was a paroxysm of coughing and the patient had a momentary sensation of a foreign body in the throat. The same evening he had an attack of dyspnea, which lasted for about half an hour and which he compared to asthma. With this there was an unproductive cough. With the coughing he had noted a certain amount of

[1] Am. Jour. Med. Sc., 1918, clvi, 625.

wheezing. On examination on December 21, 1918, the patient was propped up in bed. He had slight dyspnea but no cyanosis. On listening with the ear near the patient's mouth a wheezing sound was heard, most marked with inspiration and very slightly heard with expiration. It seemed to be rather more marked when he took a deep breath. Expansion was much less over the lower right chest. On percussion there seemed to be slightly less resonance on the right side which was most marked in the lower right axilla and back. The breath sounds in general were rather harsh, and this was more marked on the right side. No rales were heard on the left side, but there were a great many over the whole of the right lung. They were of very variable character, the majority whistling and groaning, and some with rather a wheezing character. The roentgen rays showed an artificial dental plate, apparently composed of three teeth, in the right upper bronchus. Removal was done on December 21, and immediately after it the wheezing sounds heard at the mouth disappeared. Two days after removal expansion of the two sides of the chest seemed absolutely equal, percussion was clear, no rales were to be heard and the breath sounds seemed to be equal on the two sides.

This sign appears to be of considerable value, particularly in the cases in which the foreign body does not show in the roentgen-ray plate. It has been observed in many cases and occurs with different substances. It should be listened for in all cases of obscure thoracic diagnosis in which the presence of a foreign body has to be considered.

Certain foreign bodies set up very acute and dangerous changes, among which the *peanut* takes first place. It sets up a rapid and severe reaction and the younger the child the more severe this is. The following is an example:

No. 682. The patient was a boy, aged five years, who on December 20, 1918, choked while eating peanuts. There was much coughing and gagging, with cyanosis at the time. Later the symptoms subsided, but in the evening the father noted that there was a wheezing sound at intervals, with a dry cough. Until January 7, 1919, the patient seemed well and played as usual. On this date the cough increased in severity and there was severe dyspnea, but the wheezing ceased. The physician said that air was not entering the left lung. On January 14

an attempt was made to do bronchoscopy (in another city), but without success. The patient was admitted to the Jefferson Hospital on January 16, 1919. On examination he was comfortable and showed neither distress nor cyanosis. Over the right side there were harsh breath sounds, with many medium and coarse rales. The left side of the thorax showed decided fulness, but no expansion. Vocal fremitus was difficult to obtain, but seemed much decreased. The percussion note had a curious quality of tympany, with an element of dulness. The breath and voice sounds were not heard over the left side. No rales were heard. The heart was not displaced. We considered that the peanut had acted as a ball valve and allowed air to enter but not to escape. The roentgen ray confirmed this, and after the removal of the peanut showed an equal amount of air in the two lungs.

The larynx was found to be much swollen and the trachea greatly inflamed. There was pus coming freely from the right main bronchus. The left bronchus was intensely red and swollen and contained tenacious pinkish pus. After sponging this away the peanut was seen in the left bronchus. It was removed without crushing. After removal the left side still showed decreased expansion, but harsh breath sounds could now be heard, with many loud bubbling rales. Within four days the child felt well and the signs in the chest had nearly cleared. There was still less expansion, with the percussion note and breath sounds about normal.

This case illustrates one point which may cause error—the presence of signs on both sides. This is usually due to secretions from one side being forced or carried over to the opposite bronchus. Occasionally a foreign body may be moved from one side to the other, or, in the case of a nut, portions may be broken off and carried over. It may be said, however, that there is rarely any doubt of the side involved if a careful examination is made. The decreased expansion is the most important guide in deciding this point. Special reference must be made to the need of care in the peanut cases, as a general process is set up in both lungs and the roentgen-ray plate may show more pathological changes on the side which does not contain the nut.

To this condition the term *Arachidic Bronchitis* has been applied by Jackson and Spencer.[1] They apply this term to the condition

[1] Jour. Am. Med. Assn., 1919, lxxiii, 672.

set up by the presence of a peanut in the respiratory tract, but other nuts give much the same symptoms. The clinical picture is rather a distinctive one, associated with an edematous, purulent tracheobronchitis which often results in lung abscess. The cases appear only in children and the symptoms come on rapidly, with high fever, severe toxemia and marked thoracic signs. The dyspnea is extreme, cyanosis is usually marked and there may be a purulent tenacious sputum. The fever is usually irregular, but is high for part of the day. The signs are general and are those of an intense general bronchitis, with a great variety of rales, the majority coarse and bubbling. There is decreased expansion on one side as a rule, but if portions of the nut are on both sides, as sometimes happens, this does not hold. Depending on the size and situation of the particles there may be dulness and absence of breath and voice sounds if a bronchus is plugged. The lung supplied by the plugged bronchus contains much secretion and has been described as "drowned lung." This is often mistakenly regarded as representing pneumonic consolidation. The "asthmatoid wheeze" is present in a majority of the cases. The voice is usually lost.

"We should always remember the possibility of peanut bronchitis when consulted regarding a child who rather suddenly develops irregular fever, restlessness, dyspnea with cyanosis, paroxysmal cough and the signs of a diffuse, generalized bronchitis, attended with wheezing respiration. A history of choking on a peanut or of eating peanuts at about the time of inception of the illness, renders the diagnosis almost certain." (Jackson and Spencer.)

3. As regards the question of distinctive signs of foreign bodies one speaks with great hesitation. The two signs mentioned certainly deserve careful study, namely, the presence of the fine "tissue-paper" rales over a small area and the "asthmatoid wheeze." The former has been observed with small metallic bodies only, but further observations may show that it occurs with others. They are not necessarily present in every case of small metallic bodies. The "wheeze" seems to offer more as a suggestive sign; Dr. Jackson has now observed it in over 50 cases, so that it seems to be of much importance. I venture to suggest the value of keeping it in mind and noting its presence or absence in doubtful cases.

In the very acute cases, usually due to some substance such as a nut or burr, the marked general signs may be of value, especially if there is any history. The problem is complicated by the presence of fever, which may be high, and the general picture of an acute infection. Some of these patients present a picture of the most intense toxemia. A general picture suggestive of a severe bronchopneumonia, but without any positive physical signs of it, should excite suspicion of something else.

The occurrence of signs in a lower lobe for which there is no evident explanation should always suggest the possibility of a foreign body. The same may be said to be true of local signs anywhere the etiology of which is not clearly proved.

4. As regards physical signs suggestive of a particular kind of foreign body, in the absence of a positive history one hesitates to speak with any certainty. One might *suspect* but it seems difficult to be *sure*. Evidently this is most important in the cases in which the roentgen rays give no aid. In such instances the acute general signs caused, for example, by a peanut are perhaps as suggestive as those of any group.

5. The Reduction of Errors in Diagnosis. It is evident that errors will be fewer if the possibility of a foreign body is considered. Too often it is not thought of and a hasty examination, soon after the entrance of a foreign body, results in a careless diagnosis, usually of pneumonia, which is not revised. This seems the only explanation when the changes due to a foreign body are diagnosed as tuberculosis, and this is accepted for years. In general, foreign bodies tend to go downward and set up changes in the lower lobes. It seems to take a great deal of telling to convince some of us that tuberculosis at the base of a lung alone is very rare. In every case of basal involvement, in every case of abscess and of bronchiectasis the possibility of a foreign body should be considered.

In the acute cases, typically illustrated by the reaction to a peanut, the problem may be more difficult, but the suggestions given by Jackson and Spencer are an aid. The picture is in some ways like a very acute severe bronchitis with bronchopneumonia, but it reads more like it in the description than it looks like it in the patient. It is one of the differences which is difficult to state in

words, but is suggested at once after one has seen the patients. The intense toxemia, marked dyspnea and cyanosis, and high fever without any signs of pneumonia, are points to be noted.

SUMMARY. 1. Cases of foreign body in a bronchus are not mere curiosities but are more common than we have supposed.

2. There may be no disturbance at the time of entrance of a foreign body and no suggestion in the history of such a happening.

3. Certain signs are of value, especially decreased expansion on the affected side, the presence of very fine rales and the "asthmatoid wheeze."

4. Some foreign bodies, such as a peanut, set up a very acute general process which is fairly distinctive. Other structures, such as metallic objects, cause permanent changes, usually in a lower lobe.

5. The chief errors in diagnosis are to mistake the signs for those of pneumonia in the early stages and in the acute cases, and for tuberculosis after the body has been present for some time.

PATHOLOGY OF EPIDEMIC PNEUMONIA IN CAMPS AND CANTONMENTS IN 1918

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During the year 1918, throughout which great numbers of men were gathered for military purposes in camps, there occurred a phenomenal number of cases of pneumonia not only among the crowded troops but among civilians as well.

In looking back over this period it becomes evident that this pneumonia, offering as it did a great variety of forms, did not correspond in any of its main features with the lobar pneumonia with which clinicians had been familiar before. Indeed, one receives the impression that lobar pneumonia has appeared rather rarely during this time and that it has been in a sense replaced by the other types. Much study has for years been devoted to lobar pneumonia, and it was well known as a disease beginning without definite predisposing infection or illness of another sort, caused by one of the types of pneumococcus and proceeding through a fairly constant febrile course to recovery, often after a sudden crisis, or to death. At autopsy we have been accustomed to find a broad area of uniform consolidation occupying one or more lobes or parts of lobes resulting from the even filling up of all the alveoli with a fibrinous exudate rich in leukocytes and red corpuscles. That there is much that is puzzling about the mechanism of the production of this evenly distributed exudate has long been a subject of discussion. It will suffice to say here that the form of pneumococcal pneumonia referred to as lobar pneumonia has such clinical and anatomical characters as to make it possible to outline it sharply as a definite disease. The cases arise in scattered fashion and it is only excep-

tionally that anything approaching the development of a small epidemic of true lobar pneumonia is described.

Among the many cases studied during the year 1918 there were few which presented the clinical and anatomical features of lobar pneumonia, and these occurred in about the proportion to other disease that might be found in any other year. Their relation to the time of the year and to exposure and chilling seemed to be exactly what it always has been.

But in contrast with this expected occurrence of the usual number of cases of lobar pneumonia, there arose epidemics of pneumonia of very different character which seemed to be the immediate sequelæ of other epidemics of some predisposing disease. It is difficult to say how many of these epidemics there were or how many forms of infection may have acted as predisposing influences, but it is certain that measles and epidemic influenza have been the most important of the latter. The statement is made thus vaguely because it has been maintained, not without evidence, that lesser epidemics of influenza occurred in the early part of the year long before the main and generally recognized outbreak. The majority of observers agree, however, that during the winter of 1917 and the spring of 1918, when there were great epidemics of measles, especially in the Southern camps, pneumonia was caused chiefly by a virulent hemolytic streptococcus. After a lull during the early summer there arose suddenly the great epidemic of influenza which swept through camps and civilian population from east to west, and this was followed by pneumonia caused by secondary bacterial invaders which comprised all types of pneumococcus, Staphylococcus aureus, Streptococcus hemolyticus, and the influenza bacillus of Pfeiffer.

It will be the aim of this paper to describe the forms of pneumonia caused by each organism and the modifications which result from the nature of the predisposing disease, the virulence of the bacteria, the resistance of the infected person and other less tangible factors.

It would be a relatively simple matter to describe the changes which arise in the course of a pneumonia produced by a single organism, but it must be remembered that in most of the cases several kinds of bacteria were found in the lungs. This is especially true of the cases which followed influenza. One might speak of the first

bacteria to gain a foothold after the preliminary disease had become well established as secondary invaders, the next as tertiary invaders, and so on. This is on the assumption that measles and influenza are not bacterial diseases, an assumption which we may safely continue to hold until such time as some one shall succeed in proving their bacterial nature. It appears that in each case one of these bacteria assumes a predominant role and multiplies far more rapidly than the others, and it is perhaps reasonable to suppose that it is this predominant organism which produces the inflammatory reaction and stamps the pneumonia with characters which are peculiar to its effects. But it is probable that another organism may then add features which it alone can produce or even entirely cover up with new changes the lesions produced by the first. Thus it is perhaps possible that when the predominant organism in the lung is a pneumococcus, the influenza bacillus may be present in the bronchi and cause some alteration in their walls, or that after changes in the framework of the lung have been excited by the influenza bacillus, the hemolytic streptococcus in vast numbers may spread through the whole area causing necrosis of the lung substance and a hemorrhagic exudate.

Our own studies were begun in February, 1918, in San Antonio, Texas, where we found many wards of the hospital at Fort Sam Houston filled with cases of measles. Measles had been very prevalent and there was no doubt in the minds of clinicians that the pneumonia which was proving so fatal was in a great many cases the direct sequel. Other cases did appear, it is true, in considerable numbers, with no history of measles nor of any other predisposing disease but with a story of exposure or chilling or even without that, the illness begining with headache, or nausea, cough, and epistaxis, often with pains in the chest or abdomen. But that measles played a great part was most evident to anyone who spent any time in the wards where the measles patients were collected. The onset of the pulmonary symptoms was awaited in each case with anxiety.

The sputum or smears from the throat in many of these patients showed the presence of the hemolytic streptococcus often associated with the influenza bacillus, staphylococcus, and pneumococcus We soon came to regard the streptococcus with especial apprehension,

however, for it became evident that those who harbored that organism were particularly likely to develop pneumonia. At that time the influenza bacillus was not looked upon as being of such serious import. I was ill myself for two days and my throat gave pure cultures of the influenza bacillus. Such was our very proper respect for the streptococcus that we advocated strongly the separation of those patients with measles who harbored this organism in their throats from the rest of the measles cases, being convinced that when they were housed together in a crowded ward it was a matter of only a short time before all became similarly infected so that the proportion of cases of pneumonia was greatly increased. We felt that if we could separate the clean cases of measles from those who carried and distributed the streptococcus we could save them from pneumonia. Such a separation proved impossible there, but was carried out later by Levy and Alexander with the happiest results.

In describing the conditions at Camp Pike, Opie has also emphasized the fact that the introduction of even one patient infected with the hemolytic streptococcus into a ward in which there are patients suffering from pneumococcus pneumonia will give rise to an increased mortality through the engrafting of the streptococcus upon the original condition. A patient convalescent from infection with pneumococcus of one type may in the same way be infected with a pneumococcus of another type and die.

Later, in the epidemic which occurred at Camp Dodge there was a sudden or explosive appearance of great numbers of cases of pneumonia without the coexistence of any epidemic of measles. The pneumonia was of the same type as that met with in Texas and from every case the hemolytic streptococcus was isolated, if we except a few instances of lobar pneumonia which were due to the pneumococcus. We were impressed with the idea that after long passage through many individuals the organisms thus transmitted from one person to another may have gained in virulence so as to be able to give rise to an epidemic of pneumonia without any predisposing disease. Toward the end of the epidemic a few cases of measles which had been isolated were infected and in these the pneumonia was especially severe and ran a rapid and fatal course.

Thus in Texas, and later in Camp Dodge in Iowa, we studied many cases of peculiar bronchopneumonia in which the predominant, if not the sole infecting organism, was the hemolytic streptococcus. These forms of pneumonia commonly followed or were associated with measles but there were numerous cases in which there was no history of measles. There were, of course, other cases of lobar pneumonia which were due to the pneumococcus and occurred during the epidemic just as they would at ordinary times, and these were sometimes complicated by the super-position of the streptococcal pneumonia.

While the hemolytic streptococcus was isolated from all the cases of the epidemic bronchopneumonia and appeared to be in general the predominant organism, other bacteria were also found in some cases. The influenza bacillus was present in the upper respiratory tract, the trachea and bronchi or even in the lungs in a number of the cases (16 of 49), and in one or two it appeared to be present in such numbers that a considerable part must be ascribed to it in the production of the lesions. Staphylococci, pneumococci, and miscellaneous bacteria were occasionally found in cultures from the lungs but not in great numbers except in the old cases, in some of which there was a great mixture of bacteria.

In the autopsies which we performed in these cases the outstanding feature was the occurrence of a form of bronchopneumonia in which the consolidation was nodular in character or extended along and about the bronchioles so as to present itself upon the cut surface of the lung in the form of branched, gray, opaque, projecting foci surrounded by areas of hemorrhage edema, and collapse. No single sentence can convey the manifold variety found in this lesion, which was, nevertheless, fundamentally the same throughout, although encountered in various stages and different degrees of intensity. Except in the earliest stages it was always accompanied by an effusion of fluid in the pleural cavities with a rather abundant exudation of fibrin. The most striking character of this form of pneumonia is found in the rapid infiltration of the substance of the lung tissue with wandering cells and the new formation of connective tissue in the bronchial and alveolar walls, the interlobular septa and pleura, and even in the exudate which is found in the bronchi

and adjacent alveoli. It is for this reason that the name interstitial bronchopneumonia has been applied to it.

This peculiar reaction to the presence of the streptococcus might be assumed to be the constant effect of the hemolytic streptococcus upon the human tissue, but it appears that, as in the case of the tubercle bacillus, the tissue may react in several ways to the presence of the same organism. This is shown by the fact that in certain cases in which the lesions of the interstitial bronchopneumonia were well developed there were also patches in which the alveoli of the lung were filled with an exudate of leukocytes arranged in a network of fibrin exactly as in the case of lobar or lobular pneumonia caused by the pneumococcus. Since the bacteria are present in relatively small numbers in the interstitial bronchopneumonia and restricted to the bronchi and lymphatics in the lung, and are present in great numbers in the leukocytic exudate of the lobular pneumonia, it appears that the latter is an evidence of a certain lowering of resistance on the part of the tissues. This becomes far clearer in other cases in which there is no induration of the substance of the lung and no organization of exudate but an extensive confluent lobular pneumonia with much hemorrhage in which the alveoli are filled with a fresh exudate of leukocytes, and streptococci in masses lie everywhere throughout the lung. It will be seen that these forms are comparable with (*a*) tuberculosis of the lungs with induration and encapsulation of tubercles, (*b*) similar tuberculosis with the addition of disseminated foci of caseous and gelatinous pneumonia, and (*c*) confluent or lobar caseous and gelatinous pneumonia.

To make these relations plainer it will be necessary to describe these three forms in greater detail.

INTERSTITIAL BRONCHOPNEUMONIA

When death has occurred a few days after the onset of the symptoms, as happens sometimes when a streptococcal infection of the lungs supervenes upon measles, the lungs are found distended with air, the surface smooth and the pleural cavity free of fluid. When the lung is incised, all or most of the bronchi are found to contain a purulent exudate, their walls are distinctly swollen and bordered

with a band of hemorrhage The larger bronchi and the trachea are deeply reddened Microscopically such a lung shows in the bronchi an accumulation of leukocytes with streptococci; the walls of the bronchus are infiltrated with mononuclear cells and so are those of the immediately adjacent alveoli. These alveoli contain a few leukocytes and much blood, but rarely any streptococci. At a slightly later stage the epithelium of the bronchus is often found to be necrotic and merged in a coagulum or false membrane, the wall distinctly thickened by the edema and infiltration with mononuclear wandering cells, the alveoli for a greater distance filled with rather dense fibrin, desquamated epithelial cells, blood corpuscles, and mononuclear cells. Such peribronchial areas are bordered as a rule by edema and collapse of the lung tissue.

If the process has lasted much more than a week the changes found at autopsy are far more advanced. Fluid is found to have accumulated in one or both of the pleural cavities often in very great amount. This is a thin, watery, turbid fluid with a greenish brown sediment and floating shreds of fibrin. Streptococci are present in enormous numbers. The pleural surfaces are covered with a shaggy fibrinous exudate which may be rubbed off, revealing a red velvety granulation tissue underneath. The lung when surrounded by such a collection of fluid is collapsed, airless, flabby, and dark blue, but contains palpable firm nodules of consolidation or even larger dense patches, especially in the lower and posterior portions. Much of it can, however, be distended with air forced into the main bronchus.

When incised it is found that the bronchi as before are filled with a muddy, brownish, purulent exudate rich in streptococci. The cut surface of the lung is studded with nodules which project above the surrounding lung. These are most often about pea size, but they may be much larger and sometimes become confluent. Nearly always there is about them a wide zone of hemorrhage and outside this an area of viscid edema. Closer examination shows a cross-section of a bronchiole in the center of the nodule or there is a group of nodules which are seen to surround the terminal branches of a bronchiole. Indeed if the bronchus chances to be cut longitudinally it is found that the firm tissue corresponds with a dense mantle

which accompanies it and is composed of the greatly thickened bronchial wall with the surrounding consolidated tissue.

One may see in the center the yellowish or brownish pus, then the thick gray wall of the bronchus itself merging into a rather more yellow border of densely consolidated tissue on each side. Outside this are the zones of hemorrhage and edema. The lobules are marked out sharply in many instances by the very conspicuous thickened interlobular septa which sometimes stand up like gray walls dividing the cut surface into polygonal fields in each of which there are several solid nodules. The lymphatics which belong to these septa are often very greatly dilated, and because they are filled with thrombi rich in leukocytes appear as broad, white, beaded channels almost as large as the bronchioles and occasionally much larger.

This is the usual gross appearance of the streptococcal interstitial bronchopneumonia, and microscopically there is found a great exaggeration of what has already been described for the earlier stages. The walls of the bronchi are very greatly thickened, chiefly by infiltration with wandering mononuclear cells, but also by the formation of a great deal of new connective tissue and a great increase in the vascularization. The wall, which has generally lost its epithelium, looks like a dense granulation tissue almost solidly packed with cells which have the general character of lymphoid or plasma cells. The adjoining alveoli are bounded by walls which are enormously thickened by the same process. As one passes away from the bronchus this thickening of the alveolar walls diminishes, to reappear as the interlobular septa or large bloodvessels are approached. The alveoli contain dense solid plugs of fibrin, with relatively few wandering cells and red corpuscles, but numbers of desquamated epithelial cells. Organization of this exudate and of that in the bronchi is frequent. Further away from the bronchi, red corpuscles tend to fill the alveoli and there is much fluid.

The interlobular septa are greatly widened by the spreading apart of their tissue by fluid, fibrin, and mononuclear wandering cells. Lymphatics which run in these and in the walls of bronchi and bloodvessels are distended with thrombi which are composed of a network of fibrin without special arrangement, loaded with leuko-

cytes and mononuclear wandering cells. These extend, of course, to the pleura and are almost everywhere plugged and occluded by the thrombi. The pleura, like the interlobular septa, is greatly thickened, chiefly by the growth of a layer of granulation tissue with abundant bloodvessels springing up into the overlying fibrin.

Streptococci are abundant in the bronchi, in the thrombosed lymphatics, and on the surface of the fibrin which overlies the granulation tissue of the pleura, but they are not to be found in the alveoli or anywhere else in the lung. This appears to be a matter of much importance, as may appear later. It is thought that from the bronchi they extend by a process of growth through the obstructed lymphatics to the pleura.

Other cases in which in all parts of the lung these lesions of interstitial bronchopneumonia are predominant and conspicuous may, however, present a few patches of a compact gray consolidation of the lung tissue which differs in appearance from the more familiar peribronchial nodules. These patches are found to be areas in which the relatively unchanged alveoli are filled with an exudate of polymorphonuclear leukocytes with a network of fibrin. They differ from the other areas not only in that the alveoli are filled with leukocytes instead of epithelial and mononuclear wandering cells but especially in the presence in this intraalveolar exudate of great numbers of streptococci. This is regarded as the combination with interstitial bronchopneumonia of areas of lobular pneumonia which, because they contain a luxurant growth of streptococci, seem to present the effect of a lowering of resistance.

This lowering of resistance of the host to the invading organisms goes further, however, in other cases in which there is no restriction in the multiplication and invasion of the bacteria. Instead of being imprisoned in the bronchi and carried to the pleura only by migration along the lymphatics, the whole alveolar substance of the lung is full of them. There is no barricading growth of connective tissue, no filling of the alveoli with dense plugs of fibrin which quickly become organized and strengthen the barricade, but instead, without any thickening of alveolar walls, interlobular septa or pleura, the alveoli throughout great areas are filled with an exudate of leukocytes and blood in which tangled masses of streptococci

thrive and soon bring about widespread necrosis not only of the cells of the exudate but of the tissue itself. This is a confluent, lobular, streptococcal pneumonia and appears to correspond with the lowest resistance in the invaded host. It is in a sense comparable with what is found in the lobar pneumonia caused by the pneumococcus, but is, of course, different in detail and lacks the uniform sudden spread of the process in lobar pneumonia.

In all these cases, but especially in the more acute forms, the infection of the trachea, larynx, and nasopharynx is very intense; streptococci and many other kinds of bacteria are found in quantities strewn along the surface of the mucosa. The tissue itself is very hyperemic, rather swollen, and infiltrated with leukocytes and mononuclear cells. In many instances it was noted that the voice became toneless and husky and finally all voice sounds were lost so that the patient could speak only in a hoarse whisper, or with the most violent efforts bring forth an audible sound. This aphonia seemed especially common in the severe cases which followed measles. At autopsy the trachea and larynx were deeply reddened in those cases and the tracheal mucosa was often covered with little flecks of bran-like exudate and superficially ulcerated in places. Similar ulcers of a much greater size and covered at times with a greenish pseudomembrane were found on the pillars of the fauces, the edges and base of the epiglottis, the aryteno-epiglottic folds, the mucosa of the pyriform sinuses, or within the larynx. They were especially common upon the vocal cords and in the cases of aphonia were found to have eroded deeply both cords from end to end. Occasionally the streptococci, which are abundant in these ulcers, extend into the substance of the larynx wall, causing a deep phlegmonous infiltration in those tissues.

The tonsils were not especially inflamed, and although the crypts occasionally contained masses of organisms, including streptococci, there was nothing to suggest that they had been primarily infected.

Mention has been made of the regularity with which there occurred an abundant effusion of fluid into the pleural cavities about the affected lungs and of the rapidity with which the pleura became thickened by the formation of granulation tissue. This accumulation of fluid, which soon assumed a purulent character, became the

especial concern of the surgeons, who devised various methods of treatment. There was for a time much discussion as to whether it were better to aspirate the fluid or to lay open the thoracic cavity either by an incision between the ribs or by the excision of a portion of a rib. There were advocates of both methods, since it seemed that the great object must be to remove the infected fluid as thoroughly and as quickly as possible. Difficulty was experienced in accomplishing this in some cases because of the fact that some of the exudate had become encapsulated or imprisoned between adjacent surfaces within the pleural cavity by adhesions. Even though these encapsulated pockets, which might lie anywhere but were very often found between the mesial surface of the lung and the pericardium, could be evacuated the result was often unfavorable, the patients became cyanotic and died in a sort of shock. In many other cases they died many days after the operation, usually with abscesses in the lung and with complications produced by the infection of other organs. The Empyema Commission, which worked at Camp Lee, concluded that the rapid death after the establishment of an open pneumothorax was chiefly the result of asphyxia due to the complete collapse of the lung on that side and the partial compression of the opposite one, which in a man whose lungs were already largely occluded by pneumonic exudate was too great a burden. They decided to risk the danger of the presence of the infected fluid and to operate only in a late stage when adhesions had fixed the lung to the chest wall and thereby made it difficult for the mediastinal tissue to bulge over into the opposite side when the pleura was opened. The results were greatly improved by this delay. Later, Major Evarts Graham and Captain Bell worked out this matter experimentally and found that a great effort is required to maintain adequate distention of the lung and aëration of blood when the opening is made in the chest, and that the yielding of the mediastinal tissues is such that the opposite lung is also greatly embarrassed since so much of the negative pressure ordinarily exerted on it by the chest is responded to by the bulging of the mediastinum. They found that if the opening in the chest bore a certain relation to the size of the orifice of the glottis, respiration might be successfully maintained, but that if it surpassed in size these

calculable dimensions no effort however violent on the part of the animal could maintain the distention of the lungs and aëration of the blood. When adhesions and thickening of the pleura have been produced, however, the mediastinal tissues are held more rigidly and a very much greater opening can be made with impunity. They thought the presence of the fluid with its bacteria less dangerous.

In the older cases which had survived many days it was often found that the lung, although completely collapsed, showed extremely little indication of having been the seat of a severe pneumonia. On the other hand, many presented quite large abscesses or areas of cheesy necrosis about which the consolidation was dense. These were commonly infected with several kinds of bacteria but sometimes contained streptococci alone. They appeared rather more frequently in the cases in which there was lobular pneumonia but were sometimes found in those in which only the evidences of interstitial bronchopneumonia remained. Many of these abscesses had discharged their contents through the bronchi and there remained in their place cavities with rough necrotic lining.

Occasionally such cavities communicated also with the pleura so that there was a fistulous tract extending from the bronchus to the pleura. In a few cases the bronchi throughout the lung became greatly dilated, but this, in our experience, was not a common occurrence.

The other organs of the body were surprisingly little altered in these cases. In most instances the streptococcus appeared not to invade the circulating blood, so that our blood cultures were sterile, although whenever there was a combined infection with the pneumococcus the latter organism grew out on blood cultures.

It was rare, therefore, to find endocarditis caused by the streptococcus and equally rare to find infected infarcts in the distant organs. Pericarditis with fibrinopurulent infusion was more often seen. It appears, however, that a few organisms gain the general circulation from time to time, as will be shown by the occurrence of infection with these organisms in certain places in which necrotic tissue and hemorrhage have given rise to a point of lowered resistance suitable to their growth. This is seen in those cases in which

degenerative changes in the rectus abdominis muscles are followed by rupture with hemorrhage and localization of the bacteria in the necrotic tissue.

It is difficult to understand the reason for the development of hyaline degenerative changes in the muscle fibers of the rectus muscles, but as in typhoid fever they are to be found in various stages in muscles which show no gross alteration whatever. It is only when this degeneration has proceeded to an advanced degree that some slight exertion or an attack of cough causes the muscle to tear across with the extravasation of a quantity of blood which appears as a bluish mass bulging into the peritoneal cavity and retained by the sheath of the rectus.

Microscopically the early stages show single fibers involved with a loss of the cross striations and later the collection of the substance of the fiber into formless clumps of red staining material still enclosed in the loose sarcolemma sheath. Later the nuclei of the sarcolemma seem to sink into the central mass and to multiply greatly so that a gradually disappearing clump of pink-stained material is seen to be surrounded by numbers of cells which appear to have arisen from the sarcolemma itself although it is also possible that they may be wandering cells. The intervening connective tissue increases greatly in the number of its cells, so that the whole area comes to look like a very cellular granulation tissue, in which, however, one can always distinguish the peculiar elongated groups of sarcolemma nuclei which mark the place of the original fiber. The rupture of the muscle occurs usually in a rather earlier stage and about the mass of blood are found the torn ends of the degenerated fibers. In some instances abscesses are formed in the same symmetrical way in the lower third of each rectus muscle, but the bacteria cultivated from these have proved to be pneumococci.

Another curious phenomenon which accompanied these intense infections with streptococci and pneumococci was recognized only by microscopical study. It was the cessation of spermatogenesis in the testes. Every stage in the degeneration of the epithelium of the tubules could be recognized, beginning with those in which all stages down to the spermatids are found without the formation of actual spermatozoa and ending in those in which, since mitosis

is brought to a standstill, nothing remains but the line of spermatogonia and of Sertoli cells. Still more profound changes which result in a complete hyalinization of the whole tubule are also found, but when these are in patches there may be some question as to the part played by some former infection such as mumps or syphilis. Dr. Mills will publish later a detailed report upon these changes.

The description of the pneumonia in this simple fashion may perhaps be regarded as misleading, since the complexities of the bacteriology are well known and have already been mentioned. It is true that cultures from the sputum may show a variety of organisms, often including the influenza bacillus and different staphylococci, but this might be expected since sputum passes through the pharynx and mouth in which it readily becomes contaminated. The general predominance of the streptococcus was very marked, however, and it was the only constant factor. Furthermore, its relation to the lesions in sections stained to show all the bacteria in the lung left its role indisputable, and this seems after all the only perfectly trustworthy guide as to the significance of an organism. Even so, the influenza bacillus was found in the bronchial exudate in a number of the cases, and it is impossible to say that it may not have played a considerable part in the production of the lesions, especially as in one case the streptococci were very few, so that the Gram-negative bacilli held the predominant place. In this case, too, the lesions were strikingly like those which we found later in cases in which the influenza bacillus was present in pure culture.

The pneumococcus in this epidemic was always associated with lobular pneumonia, but it could be overgrown by the streptococcus, and in several cases, although it was cultivated from the circulating blood and persisted in the distant organs and in endocardial vegetations at the autopsy, it could not be cultivated from the lung. Nothing but the hemolytic streptococcus grew there, although the pneumococci were still recognizable in great numbers in the sections.

Once or twice we found such a combination of infections that in the same lung there was lobar pneumonia in one lobe with living pneumococci, and an interstitial bronchopneumonia in the rest of the lung with streptococci. These lesions seem not to have overlapped, and it was remarkable that in the area of lobar pneumonia

there was no induration or infiltration of the framework or pleura, while immediately on passing over into the other area where the streptococcus prevailed the pleura became thickened with a layer of granulation tissue, and the interlobular septa and bronchial walls stood out with unaccustomed prominence as dense walls. In these cases the pneumococcus had circulated in the blood, but no streptococci could be found there until just before death. After death, of course, the heart's blood contained them.

But no matter what the complexities and variations of these cases, they allowed themselves to be analyzed into those caused by the pneumococcus, which were lobar pneumonias, and those caused by the hemolytic streptococcus, which were of these types: interstitial bronchopneumonia, interstitial bronchopneumonia with patches of lobular pneumonia, and confluent lobular pneumonia without any change in the framework of the lung. The influenza bacillus was present in a few cases, and may have been the exciting cause in one or two. The streptococcus was present in all cases, and was often in pure culture, as shown by all bacteriological methods and by the study of the bacteria stained in sections, which latter method demonstrated its causal relation to the lesions most convincingly. How measles affected the respiratory tract is not known, but it is certain that it predisposes to the streptococcal pneumonia, and that the lesions are more rapidly developed and more severe in the cases in which it has preceded the pneumonia than in those others which started in its absence.

The second epidemic began, as every one knows, in the late summer and early autumn, and spread like the most grim pestilence that has ever been described over the whole continent, and indeed over the whole world. Hundreds of thousands died in this country from the pneumonia which followed close upon it, and there seems to be nothing which has far surpassed it in its destructive effect. Of course, the idea which has somehow come into existence in the minds of the laity that it was, in truth, the pneumonic plague such as ravaged Manchuria some years ago, it entirely absurd. It would not have been possible to miss the plague bacillus in cultures from the very first case, nor to have failed to distinguish its peculiar

distribution in the lungs when they were studied at autopsy. Far from being a disease so easily studied bacteriologically and pathologically as the pneumonia caused by the plague bacillus, the cause of influenza is still unknown. In spite of the extraordinary opportunity given to all the scientists of the world to study this disease, and in spite of the great amount of work done in striving toward some elucidation of the cause, no credible statement has been made as to the nature of the living virus, as to its mode of transmission, or as to the anatomical lesions that it produces.

It is true that we state confidently that it is transmitted from infected to healthy persons by a spray of droplets exhaled with the breath, and received in the respiratory tract of people who come near, but we have no proof of this, nor of any other method. No one has died of influenza, so far as is definitely known, although the reports from various cities give figures which would indicate in some cases that great numbers died of influenza, smaller numbers of pneumonia, in other cases about the same number of each. Every one who died in the course of the epidemic disease was found, when there was an autopsy performed, to have died of pneumonia. It was for this reason that no one has observed the anatomical lesions produced by the epidemic disease influenza.

It is known, however, that there are many reasons for believing that this disease is not primarily a disease of the respiratory system, but rather a generalized infection. There are cases in which no respiratory symptoms develop, but which throughout show evidence of some general intoxication or infection which causes great depression, aching, and malaise. Others develop intestinal disturbances with diarrhea, which ultimately pass off without any coryza or cough.

In all the cases there was, however, a change in the biological relation to bacterial infection, such as to lower the powers of resistance to a degree scarcely to be paralleled in any other disease. An index of this is found in the usual leukopenia, which persists in spite of the invasion of bacteria and the development of pneumonia.

The pneumonia was due to the secondary invasion of many kinds of bacteria, including especially, however, the various types of pneumococcus, the hemolytic streptococcus, the staphylococci, and

the influenza bacillus. Several of these organisms might invade at once or in succession. The influenza bacillus was searched for with great diligence because of its name and its supposed causal relation to the epidemic disease, and it was found in a great number of cases, in some places in every case, less commonly in other places.

There has been much discussion as to its actual significance, and at first many of those who found it so regularly insisted that it was the cause of the epidemic disease influenza, and were intolerant of any one who failed to find it. But recently it has become rather difficult to find a supporter of this view, and nearly every one has come to look upon it as a common and important pathogenic invader of the lungs, but strictly as a secondary bacterial invader, responsible for the pneumonia it may be, but not proved to be the cause of the primary epidemic disease. It is known to be a common inhabitant of the throats of normal persons, and might be expected to occur with increased prevalence among people whose resistance was lowered by such a disease as epidemic influenza, just as the pneumococcus and other organisms were found in greater numbers in these throats.

Bloomfield has felt, as we have ourselves, that the epidemic influenza has many points of resemblance to measles, and that the mechanism of predisposition to secondary pneumonia is quite similar, but greatly intensified in its effects. He has observed a characteristic enanthem in the mouth and pharynx, and a less characteristic but very distinct exanthem or rash in many cases, and has based his belief in its relation to the common exanthematic diseases largely upon these facts. He has also noted the fact that, as in measles, the skin reaction which should follow the von Pirquet test is absent during the height of febrile illness in influenza but comes out brilliantly as soon as the fever is over.

Our own experience has been chiefly with the anatomical and bacteriological investigation of the forms of pneumonia which accompany and follow influenza, and these we have studied at Camp Lee, in Virginia; at Camp Dix, in New Jersey; and at Johns Hopkins Hospital, in Baltimore. At Camp Lee we worked at the height of the epidemic, at Camp Dix the influenza itself had just ceased, and there remained cases of pneumonia which were consequently in a

somewhat later stage. At Baltimore our material for study comprised all the cases dying at the hospital throughout the epidemic.

At Camp Lee and in Baltimore we found in the fresh cases a pneumonia which was sometimes very sharply lobular in its distribution. In many cases the consolidated lobules stood out with extreme distinctness, separated by air-containing or collapsed lobules so as to present a checkerboard appearance over the pleura and even on the cut surface. But in most instances the areas of consolidation were not so limited, but became confluent throughout several lobules, ultimately involving most of a lobe. In these fresh cases the consolidation presented peculiarities which we have all despairingly attempted to recall in words. It was evidently seen in identical form by most of those who studied these cases, and was clearly a very rapidly produced condition, to be found only in those who succumbed after a short illness. There was no effusion of fluid into the pleural cavity, the surfaces were smooth except for patches of opaque bloodstain, like dull red paint, on the surface. The bronchi contained only a brownish, frothy fluid, and their mucosa was pale. The lung was evidently consolidated and airless in part, especially in the posterior and lower portions of its lobes, and on section these areas were found to be swollen, firm and elastic, but smooth, moist, dark red, and elevated above the surrounding surface, into which they sloped off through an edematous zone. No plugs of opaque rigid exudate were to be seen in alveoli or bronchioles. Instead, there were little depressions like pinholes everywhere, filled with a red gelatinous fluid and separated by thick, slightly firmer lines of lung tissue. These proved to be the dilated ductuli alveolares separated by areas of distended alveoli. The whole area oozed bloody viscid fluid and the change has been spoken of as hemorrhagic edema, but it was more than that, although compact plugs of exudate had not yet formed.

Microscopically, the alveoli are found to be filled with the freshest possible delicate network of fibrin entangling red-blood corpuscles, leukocytes, and mononuclear cells, many of which are desquamated epithelium. Every cell in this exudate is perfectly preserved, and

in the millions of red corpuscles not even a crenated cell appears, so that the exudate must have reached the alveoli a very short time before. The bronchioles and ductuli alveolares are filled with fluid which gives with the fixing fluid only a delicate fibrillar coagulum. The walls of these bronchioles and ductules are overlaid by a curious hyaline material which is not fibrin and which extends down into the mouths of the atria.

It is, therefore, an extremely fresh pneumonia, qualitatively, but not in distribution like the rather hypothetical stage of engorgement which precedes red hepatization in lobar pneumonia. The dilatation of the ductuli alveolares and minute bronchioles with gelatinous fluid is peculiar, and so, too, is the laying down of a hyaline layer over the epithelium of the bronchioles. Scattered through all the exudate, whether in bronchioles or alveoli, are pneumococci, sometimes fairly numerous, sometimes in incalculable numbers, so that every phagocytic cell is loaded with them and there are millions free in the alveoli. In a great many cases there are absolutely no other organisms in the lungs—culture, mouse inoculation smears, and, best of all, careful staining of the sections for bacteria showed this. It is possible to scan these sections for Gram-negative and Gram-positive bacteria, so that scarcely one Gram-negative organism need be missed, and certainly no significant number of influenza bacilli could pass unseen. Everywhere the pneumococci are in intimate relation with the lesions, and are evidently the cause of the pneumonic inflammation.

This may serve as a description of the early stage of a pneumonia caused by the pneumococcus. It is probably the same whether the organism be of Type I or Type IV. Later stages show a further confluence of the consolidated areas, and before very long the appearance of definite opaque and rigid plugs of exudate in the alveoli. Hemorrhage continues to be predominant, however, and at all times it seems that one may discern the spaces of uninvolved lung tissue between the areas of consolidation. Pleural effusion is still absent, although the pleural membrane itself is often fairly packed with bacteria which appear as grayish-yellow patches.

The striking feature is the phenomenal multiplication of bacteria in the non-resistant lung, which proceeds so rapidly that in the lack

of many phagocytic leukocytes those which do appear are soon filled to their capacity, while most of the organisms remain free.

In some instances the hemolytic streptococcus was found to be the predominant organism, appearing in incredible numbers in the lungs and bronchi, and outgrowing all other bacteria which may have been present. Then the gross appearance of the respiratory organs was somewhat different. There was no great pleural effusion, since death occurred too quickly to allow of that, but a thin, bloodstained layer of fibrin covered the surface with patches of brownish opacity, and a small amount of bloody fluid was found in the pleural cavity. The lungs were very voluminous and heavy, and bloodstained fluid ran from the bronchi. The anterior portions were usually air-containing, but the whole posterior part was consolidated. On section the consolidated areas were almost black, uniform in appearance, and moist except where grayish brown patches seemed somewhat dryer and still more opaque. It was difficult to see the outlines of lobules or any of the framework of the lung in such areas. The surface of the consolidated area was rather spongy, without any definite alveolar plugs of exudate. The bronchi were deeply bloodstained.

Microscopically, such a lung shows a loose edematous exudate of fibrin with leukocytes, and a great quantity of red-blood corpuscles in all the alveoli and bronchi, with very numerous streptococci in chains and pairs. Most of these are not inclosed in phagocytes, but lie scattered free in the fluid. They are so extremely numerous that the recognition of their presence in the tissue of the interlobular septa, lymphatics, etc., seems hardly worth while. They pervade everything, and it is not surprising to find that great areas of the consolidated lung have become completely necrotic. Indeed, it is only in the rather marginal portions that the character of the exudate can be made out clearly, for elsewhere it is all merged into the necrotic mass which includes the whole tissue of the lung. In the alveoli within the necrotic areas the streptococci form a tangled mat or feltwork which fills up most of the space. They have grown there as though in the most favorable culture medium in a thermostat.

Intense inflammatory changes in the bronchi, trachea, larynx, and pharynx, are accompaniments of this pulmonary lesion.

It will be observed that this condition corresponds very well with that which we observed in the first epidemic, and described as confluent lobular pneumonia due to the streptococcal invasion of persons of low resistance. The effect of the extreme lack of resistance following influenza makes the rapidity of the invasion even more striking here.

Such were the cases observed at Camp Lee and in Baltimore. There were cases also in which *Staphylococcus aureus* appeared to be the predominant organism, and in these it was once associated with the influenza bacillus. This case presented a pneumonia rather like that produced by the pneumococcus as described above, but nothing can be determined from one case, and Dr. Chickering, who found many cases with predominant staphylococcus infection, has studied the type of pneumonia produced by it most carefully.

We were surprised to find at Camp Dix cases of a quite different character. There were a few which resembled those described above but in many cases there was no such edema and hemorrhage throughout the lung as we had found at Camp Lee. Instead, the lungs presented the following appearances:

The pleural cavities contained no fluid, but the pleural surfaces were adherent or covered with a thin layer of fibrin. The bronchi were pale, and exuded a thick, sticky, yellow pus. The lungs were pale, and rather distended with air, but throughout their substance could be felt many shotlike nodules and firm areas of rather larger size On section the whole cut surface was pale and rather dry, and there projected everywhere firm, yellow nodules with smooth, dense, shiny surface or larger area of similar grayish yellow, firm tissue. In the center of many of the nodules could be seen the lumen of a bronchiole exuding a tiny droplet of pus.

The bronchi, trachea, and larynx were pale, but covered with a sticky mucopurulent exudate. This exudate, whether from the bronchioles in the lung or from the trachea, was rich in influenza bacilli. In two cases these were in pure culture, as shown by bacteriological methods and by the staining of the bacteria in sections of the lung. In several others cases the bacillus of Pfeiffer was the predominant organism, although there were other bacteria in small numbers in the lungs.

In every case studied at Camp Dix the influenza bacillus was found either in the lungs or in the upper respiratory tract or nasal sinuses.

Microscopically, the changes in such a lung reminded one at once of those in the interstitial bronchopneumonia caused in the former epidemic by the hemolytic streptococcus, and it is indeed an interstitial bronchopneumonia.

The bronchiolar walls are greatly thickened by infiltration of mononuclear cells and by an enormous new formation of connective tissue. Leukocytes are abundantly strewn through these walls also, and extend into the walls of the adjacent alveoli.

The bronchi are filled with an exudate of polymorphonuclear leukocytes, many of which are loaded with influenza bacilli, while numerous bacilli lie free in the fluid. The adjacent alveoli contain leukocytes, with some fibrin and epithelial cells, but no conspicuous hemorrhage. Instead, the exudate is rapidly undergoing organization, and the strands of connective tissue add to the density of the nodule. The alveolar walls are very greatly thickened, partly by the leukocytic infiltration referred to above, partly by the inwandering of mononuclear cells and the new formation of connective tissue. The walls of bloodvessels, the interlobular septa and the pleura are all moderately thickened in the same way. The change differs from that produced by the streptococcus in several ways. The influenza bacilli are restricted to the bronchi, and do not appear in the alveoli, the lymphatics are quite inconspicuous, and are not found distended with thrombi laden with bacteria, and the pleura is not infected as in the streptococcal pneumonia. The absence of great pleural effusions of fluid makes these cases very different from those caused by the streptococcus. Organization of the exudate is a far more striking feature in the pneumonia caused by the influenza bacillus than in the streptococcal form.

The opinion was expressed that such an interstitial bronchopneumonia, when caused by the streptococcus, represented a rather unsuccessful invasion by that organism stoutly resisted by the forces of the body.

A somewhat more successful invasion would show, side by side with the interstitial changes, certain patches of alveoli filled with an exudate of leukocytes with very numerous streptococci.

In the cases of interstitial bronchopneumonia caused by the influenza bacillus the bacilli are even more sharply restricted to the bronchi by the dense barricade, so that this may be looked upon as an even better example of a stoutly resisted invasion. But there are some cases in which a few patches of alveoli contain a leukocytic exudate loaded with influenza bacilli. This must represent a distinct local victory on the part of the bacilli. In none of our cases, however, was the resistance of the host so lowered by the epidemic disease influenza as to allow the influenza bacillus to invade easily and to produce a widespread intra-alveolar exudate. If we can trust to our observations, the influenza bacillus is not so virulent an organism as the streptococcus. In any one person with resistance depressed by an attack of influenza, secondary invasion of the streptococcus would produce an extensive hemorrhagic intra-alveolar exudate with millions of bacteria, while secondary invasion of the influenza bacillus would succeed only in causing a bronchitis and peribronchitis with induration of the lung. It must be a great lowering of resistance which allows the influenza bacillus to stir up patches of an intra-alveolar exudate in which it still thrives. One receives the impression that the lowering of resistance after measles is rather less than after influenza, for after measles most of the streptococcal infections ended in an interstitial bronchopneumonia, but after influenza all of them produced a devastating confluent pneumonia, with hemorrhage and necrosis. Even under these latter conditions the influenza bacillus produces only an interstitial bronchopneumonia. I suppose this must indicate a relatively low virulence for the influenza bacillus as compared with the streptococcus, and perhaps explains the rarity of influenza bacillus pneumonia under ordinary circumstances and the failure of the influenza bacillus to invade except in the train of some predisposing disease.

To summarize, we may say that in the second epidemic the country was swept by a disease long familiar as epidemic influenza, but still of unknown etiology.

The anatomical changes produced by this disease have not been seen by any one; at least they have not been clearly recognized, but every one has realized that the disease produced an extraordinary depression or lowering of the ordinary powers of resistance, so that

these persons were intensely predisposed to the invasion of any pathogenic bacteria which happened to prevail in their mouths and throats. Pneumonia, therefore, often followed immediately, and all who died showed the pneumonic changes in their lungs, changes which were exceptionally severe and rapidly fatal, on account of the unparalleled spread of the bacteria in the unresisting tissues.

But the type of pneumonia was different according to the organism which happened to invade, and it was possible to recognize pneumococcal, streptococcal, and staphylococcal forms of confluent lobular pneumonia and to distinguish them from each other and from the interstitial form caused by the influenza bacillus of Pfeiffer.

Stress must be laid upon the epidemic character of the secondary invasion, which made it appear that in one camp nearly every case presented a pneumococcal pneumonia, while in another almost every case was due to the influenza bacillus. It is not surprising that with the one-sided view obtained at first by those who observed these cases in one hospital only, there should have been announced the conviction that the bacillus of Pfeiffer was the cause of the primary disease as well as the pneumonia. But broader experience has shown, it seems, that this prevalence of the influenza bacillus in some camps, as in those of the New England States, represented a local condition. In other places, pneumococci and streptococci were the opportune invaders, and we are still quite ignorant of the cause of the primary disease.

LETHARGIC ENCEPHALITIS: HISTORY, PATHOLOGICAL AND CLINICAL FEATURES AND EPIDEMIOLOGY IN BRIEF

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Introduction. It is of more than ordinary interest that within the past dozen years at least two epidemic diseases, affecting chiefly the central nervous system, have prevailed widely in Europe and America. The first of these diseases is poliomyelitis, which since 1907 has passed through several phases in the United States and culminated in the outbreak of unparalleled severity, centering in New York State, in 1916. The second is lethargic encephalitis, apparently only recently introduced in and already widely distributed through this country. It is highly desirable that the main facts known about the latter disease should be given publicity, and it may well be that the experience, often of tragic nature, gained with poliomyelitis may serve us in dealing more effectively with the encephalitis peril. Hence I shall, by way of introduction to the main theme of this paper, sketch the recent history of poliomyelitis.

The occurrence of poliomyelitis in America, and generally in Europe, beginning in 1907, followed, it now appears, the severe epidemics of Norway and Sweden which reached a first climax in 1905. Indeed, poliomyelitis became so widespread after 1905 that it may be regarded as having become pandemic. Besides Europe and the United States, South America, Australasia and the far eastern countries all were involved.

Poliomyelitis, it is true, had been mildly epidemic in the United States before 1907, but the most severe of the earlier outbreaks were

inconspicuous as compared with the later ones, both as regards the number of persons affected and the territory invaded. Thus the severe Vermont epidemic of 1894 included 130 cases; and it is worth noting that no extension into distant territory followed in its wake.

It is customary to ascribe to Wickman, who studied the Swedish epidemic of 1905 and gave to the world in 1907 his remarkable book on *Epidemic Poliomyelitis*,[1] the first account of the so-called abortive cases of poliomyelitis. But Caverly, who studied the Vermont outbreak,[2] clearly described cases which did not go on to frank paralysis but terminated in prompt recovery after symptoms which seemed to presage the onset of paralysis.[2] As these "imperfect" or non-paralytic instances arose, along with the frankly paralytic cases, it seemed to Caverly that they belonged in the same category with the latter.

This conception is now abundantly justified, and it is due to Wickman that the abortive type of cases of epidemic poliomyelitis is so widely recognized. The epidemiological significance of the abortive cases is considerable, since many of them are ambulatory and most are invalided for a few days at most, and they thus furnish ready means of distributing freely the inciting microbic agent or virus of poliomyelitis in their surroundings. From the public health point of view the abortive and ambulatory cases of poliomyelitis are more dangerous than the frankly paralytic, since by the very nature of the circumstances the latter are restricted in their contact with healthy persons.

We may think that the forerunners of these epidemics of poliomyelitis were imported into the United States about 1906 or 1907; that the cases of the disease or carriers of the virus first had merely local distribution, but that gradually the conditions favoring a wider spread of the disease became more extensively developed; that thus the more numerous and severer outbreaks arose; until finally conditions in certain localities having become highly favorable, the terrific explosion with its thousands of paralyzed cases occurred in 1916, since which time the disease, while still present, has reverted to a relatively quiescent state.

The medical profession in general in the United States in 1907 was not informed and ready to deal with the epidemic of poliomye-

litis. Practically none of the profession had had previous experience with the disease, except in its rare sporadic form, which at first seemed improbably connected etiologically with the epidemic affection. Few physicians knew of the succession of outbreaks, small and large, which for many years had been going on in Norway and Sweden. When, therefore, the epidemic appeared in the United States there was inevitable confusion of diagnosis, lack of understanding of the infectious nature of the disease and the degree of its communicability, uncertainty as to the public health policy to be pursued, and, finally, in places an undue harshness in the endeavor to curtail its ravages.

Gradually a deeper knowledge by the profession at large of the disease has removed many of these disabilities, and a wider understanding of its atypical forms is rendering feasible the early and more complete institution of those protective public health measures, with which hope of better control of epidemics is inseparably connected.

Historical. With this introduction before us we shall now consider certain historical points regarding lethargic encephalitis. It appears that the first cases of that disease recognized in the United States occurred in the winter of 1918–19. In contradistinction to epidemic poliomyelitis there is no reason to suppose that this epidemic affection of the central nervous system ever before existed in America. This point is an important one. At present the disease seems to be widely distributed, as cases have been reported from many States.

It is possible to trace the cases of lethargic encephalitis, or, as it is also called, epidemic encephalitis, now arising in this country, to an outbreak which occurred in Vienna and neighboring parts of Austria in the winter of 1916.[3] Because of war conditions, knowledge of this unusual disease did not at once reach Western Europe and the United States, but, nevertheless, cases of the disease arose in England and France in the early months of 1918 and in America about one year later.

Both in Austria and in England, in which countries the first cases were observed respectively in Eastern and Western Europe, the disease was first mistakenly attributed to food intoxications. In

Austria the early cases were ascribed to sausage-poisoning, in England to botulism arising from various foods.[4]

This error is not perhaps as remarkable as might at first sight appear. In the first place both countries were laboring under unprecedented conditions of food shortage—Austria because of the blockade, England because of the submarine. Moreover, because of this shortage, preserved foods were employed on a scale never before equalled, and, of course, waste and refuse were reduced to a minimum. Furthermore, an early symptom of this encephalitis is third nerve paralysis—giving rise to diplopia, ptosis, etc.—which happens also to be an early symptom in certain forms of food-poisoning and notably in botulism.

Ultimately in both countries the notion of food origin became untenable and the disease was recognized as arising independently of diet and other usual conditions of life, and came to be viewed as probably of microbic origin and of communicable nature.

Pathological. The first fatal cases, which occurred in Vienna, supplied on histological study a physical basis for the symptoms observed during life, and the first English and French cases similarly examined microscopically showed lesions identical with those described for the Austrian cases. In due time the anatomical study of cases arising in the United States and still other countries showed close agreement with the others, and now a histological basis of the pathology of the disease, of remarkable concordance, has been provided. On this basis we may now regard lethargic encephalitis as representing a definite pathological as well as clinical complex, and to consider it as a distinct disease.

The histological changes or lesions of lethargic encephalitis may be both extensive and profound. Those so far described as confined to the central nervous system affect particularly the brain, and especially the gray matter at the base of that organ. While, indeed, any part of the gray matter may be involved, and lesions are found in the cortex and in the cerebellum, the structures particularly affected are those about the third ventricle, the aqueduct of Sylvius, the lateral ventricle and optic thalamus, and the pons and medulla. The spinal cord is variably involved. In general, it may be stated that the severity of the cerebral lesions diminishes

from before backward; the upper or cervical cord often shows changes; but it is still to be determined how often and to what extent the cord, as a whole, is affected.

The lesions themselves consist of cellular aggregations about the bloodvessels, cellular infiltrations in the nerve tissues themselves, small, often microscopic hemorrhages, and an outpouring of plasma or lymph into the tissue interstices (edema). The cellular accumulations and invasions are chiefly of mononuclear nature (lymphocytes, plasma cells, polyblasts); polymorphonuclear cells are also met with but relatively are inconspicuous. The lesions themselves occur in nodular and in diffuse forms, and those of the tissues are at times clearly associated with the vascular affections and at other times are so extensive as not to be brought into relation with particular vascular involvements. The paralyses of the ocular, facial and other muscles which sometimes occur arise, with rare exceptions, from the cellular and other invasions of the nuclei of the corresponding nerves.

Clinical. The clinical phenomena or symptoms of lethargic encephalitis are referable to the lesions of the central nervous organs or the pathological process as sketched. It is perhaps too early in the study of the disease to set up hard and fast clinical varieties or types. However, attempts at classification have already been made. One of the most comprehensive is that of MacNalty,[5] which is reproduced here, as it is suggestive and may prove useful in practice. MacNalty distinguishes six groups of cases, as follows: (1) Cases with general symptoms and without localizing signs. (2) Cases with third nerve paralysis and general disturbance in the function of the central nervous system. (3) Cases with facial paralysis and general disturbance in the function of the central nervous system. (4) Cases with spinal manifestations and general disturbance in the function of the central nervous system. (5) Cases with polyneuritic manifestations and general disturbance in the function of the central nervous system. (6) Cases with mild or transient manifestations (so-called "abortive" cases). To these should be added cases of paralysis of other motor cranial nerves than the third and fifth, such as those of deglutition and respiration.

Probably there is an incubation and prodromal period which precedes the onset of the striking subjective and objective symptoms of the disease; but thus far these have not been clearly defined. Hence the so-called onset of the disease is usually described as sudden or acute. This latter is indeed so striking that the patient is able often to tell the precise hour of a particular day on which he fell ill. Actually the striking symptoms often develop more slowly than in poliomyelitis.

The initial symptoms are described as chills, lassitude and general malaise, headache and general pains, nausea and anorexia, associated often with the common symptoms of upper respiratory catarrhal affections. Fever is an irregular manifestation. It may be present at onset or may appear only later. The temperature range tends not to be high—101° or 102°—but it sometimes swings to 103° or 104°. As the symptoms develop there arise lethargy or drowsiness, vertigo, tinnitus, muscular weakness, blurred or misty vision, diplopia, photophobia, tremors and twitchings, ataxia, delirium, irritability, restlessness, mental depression and other alterations, difficulty in articulation and in swallowing, stiffness of neck and spasticity of other muscles, sweating, hiccough, etc. Among the earliest symptoms to arrest the attention of the patient and the physician are diplopia and ptosis, with varying degrees of lethargy. But still other paralyses (*e. g.*, facial) may appear, and the lethargy may arise independently of all localizing nervous signs.

The outstanding feature of the disease is the lethargy, which is progressive in character and present in the great majority of cases (80 per cent. ?). It may appear suddenly but usually is gradual in onset. The patient becomes apathetic and dull, appears dazed or stupid, the hours of sleep become prolonged and he is hard to wake in the morning. Moreover, he may fall asleep at odd hours—while engaged at work or at meal times. The lethargy may deepen into stupor or even into coma. Its duration is variable—a week, a month or even longer—up to four months. Even after long periods recovery may still follow. During the lethargy there may be lack of facial expression (mask-like features). The usual state is one suggesting profound sleep, from which the patient can be

aroused by loud speaking, prodding, etc., to partake of food or answer questions. But cases in which marked restlessness and even mania have been present, followed by lethargy, have been noted.

Symptoms referable to irritations of the meninges appear. Usually they are slight, and while sometimes arousing suspicion of acute meningitis, that condition is excluded by lumbar puncture and examination of the cerebrospinal fluid. The fluid tends to be under somewhat increased pressure, but clear. The number of cells is slightly increased (very rarely 100 per cubic millimeter) and the globulin content little and sometimes not at all excessive. The cells, which range usually around 10 to 20 per cubic millimeter, consist partly of mononuclear and partly of polynuclear leukocytes. In addition the important point of rare presence of Kernig's sign should be mentioned.

The occurrence of paralyses of the face muscles has been mentioned. Paralysis of the extremities is rare; wrist-drop has been noted at least in one instance. But a far more common symptom is rigidity or spasticity, chiefly of the extremities, which in a few cases has been observed to extend to the spinal and even the facial muscles, making a picture suggestive of paralysis agitans. This spasticity of the extremities is ascribable to involvement in the encephalitic process of the lenticular nucleus and the corpus striatum.

The duration of the stupor is very variable; it may last a few days, for weeks or even for months, and recovery still take place. The return to clear mentality is usually gradual; muscular power also tends to return slowly, and general convalescence tends to be prolonged. In paralytic examples of the disease, rapid, complete or partial clearing of the palsies has been noted.

The number of cases of undoubted lethargic encephalitis thus far reported is too small to indicate the age periods of greatest incidence. For the present it may be stated that the disease occurs at all ages, namely, from a few months to advanced years (over seventy). Likewise it appears as if the two sexes were about equally attacked.

The fatalities reported range from 20 to 35 or 40 per cent. Probably the higher mortalities refer to groups of the severe cases of the

disease. Since knowledge of the disease is still very restricted and diagnosis still in its beginnings, probably many cases of lighter affection are overlooked or given other names and interpretations, thus making it impossible to arrive at present at an accurate estimation of the prognosis and mortality. At best, however, the disease is to be regarded as serious, whether from the point of view of long duration from onset to restoration to health, or of fatality. The chief immediate causes of death reported have been intercurrent pneumonia and paralysis of the respiratory center in the medulla.

Present indications are that the degree of communicability of or susceptibility to lethargic encephalitis is low, possibly equalling that of epidemic poliomyelitis as observed in ordinary times. The seasonal incidence seems to be mid-winter, in that respect resembling epidemic meningitis and differing widely from epidemic poliomyelitis, which prevails usually in mid-summer and early autumn.

Explanations of the lethargic state have been offered. A toxic origin is, of course, possible. It seems more likely, however, in view of the nature and distribution of the lesions, that its source is rather a mechanical one. It is known that the sensory stimuli from the special and other senses pass by way of the thalamus to the cerebral cortex.[6] Since, therefore, the thalamus is so commonly the seat of the cellular infiltrative lesions described, it would appear that the stimuli are interrupted in that organ on the way to the cortex, whence a kind of sleep supervenes. The obstruction to the stimuli is not absolute, since the patient can be aroused by increasing their intensity (as by loud speaking, prodding, etc.).

Epidemiological. It is now sufficiently obvious why the popular name of "sleeping sickness" has been applied to this malady. The disease is, of course, wholly distinct from African sleeping sickness, which is a trypanosomal infection carried from person to person by means of an insect vector—the tsetse fly.

When a disease apparently new arises it is always important to inquire whether the particular set of symptoms which are taken to characterize it has been observed and recorded before.

In the present instance there are two significant records which may easily refer to a similar and possibly identical disease. The

first one dates from 1712 and refers to an outbreak of so-called sleeping sickness centering about Tübingen in Germany. The second record dates from 1890 and deals with a rather puzzling malady, called "nona," which is described rather in the lay than the medical literature of the time and seems to have prevailed in the territory bounded by Austria, Italy and Switzerland. In respect to neither instance do the records contain the minuter data which would admit of a certain identification of the disease described with the encephalitic malady we are considering.

One circumstance is, however, significantly suggestive. The location of the 1890 affection "nona,"[7] which was characterized by somnolence, stupor and coma, coincides roughly at least with that of the first cases reported in the present epidemic. The question may, therefore, well be raised whether the endemic home of this epidemic variety of encephalitis may not be that corner of Southeastern Europe overlapping the three countries mentioned. If this should prove to be probable, the next questions to arise would relate to the circumstances under which the disease slumbered on in ordinary times and to the conditions favoring a greater activity and wider spread about the year 1916.

To deal with the first one will require particular and intensive studies carried out with the special object in view to disclose hidden cases in the region originally affected. An answer can in the meantime be hazarded to the second question. The depressing effects of war, acting by way of hunger, cold, migrations of populations and general insanitation, might initiate the conditions through which a low endemic might well be converted into a higher epidemic incidence of the disease.

In effect a similar set of depressing and favoring conditions may be supplied by a highly debilitating and destructive epidemic such as the periodical waves of pandemic influenza which recur from time to time. In this manner may possibly be explained the coincidence of the Tübingen epidemic of 1712, also called sleeping sickness, and of the nona of 1890, with epidemic influenza, just as the wider distribution of the encephalitic malady and the influenza epidemics of 1918 and of 1920 may be similarly associated. In other words, what the depressing circumstance of the war did

for Austria-Hungary in 1916 the pandemic of influenza may have done for the rest of the world in 1918 and subsequently, namely, prepare the soil, as it were, for the growth in number of cases and for increases in intensity and capacity for spread of an infectious nervous disease ordinarily narrowly localized and moderately benign.

This relationship of lethargic encephalitis to the epidemic of influenza has indeed led to a discussion as to whether the former is not merely a sequel—early or late—attending a certain, if only small number, of cases of epidemic influenza.

Regarded merely chronologically the question presents itself as follows: In 1916, when the first cases of encephalitis appeared or at least were recognized in Austria, the epidemic of influenza which prevailed later in 1918 had not yet been noted. In the instances of England, France, the United States and some other countries the epidemic influenza and cases of lethargic encephalitis were more or less coincidental. Since influenza varies so much in degree of severity it is of little moment to debate whether victims of the encephalitis had previously suffered from influenza or not.

On the other hand, there is no recognized numerical relationship between the extent of influenza and the number of cases arising, or at least identified, of the encephalitis. It is, of course, true that encephalitis has long been recognized as one of the sequels of epidemic influenza. Indeed, in the etiology of encephalitis, influenza occupies a prominent place; but in no other pandemic of influenza has this remarkable association of encephalitis occurred with certainty. Little weight can be given the supposed coincidence of influenza and the "sleeping sickness" of 1712, and it is highly improbable that the semimysterious affection, "nona," which dates from 1890, should have taken its origin from the influenza epidemic in Southeastern Europe at that period and the association not have been observed elsewhere in Europe or even in America at the same time as a concomitant of the influenza epidemic, which raged with great intensity in those countries. Moreover, the occasional cases of encephalitis definitely observed to follow attacks of influenza have presented a more hemorrhagic character and sometimes have been attended by Pfeiffer bacilli in the nervous tissues and meninges, which is not the case in the lethargic disease we are now considering.

Finally, should the reported experimental transmission of the encephalitis to animals be confirmed, a further distinction from the influenzal variety will have been established. Therefore the outbreak of lethargic encephalitis either antedated (Austria) the pandemic of influenza of 1918, or (in other countries) the two diseases more or less overlapped, that is, although probably quite by accident, prevailed concurrently. It is desirable, for the time being at least, to regard them as independent diseases.

The history of lethargic encephalitis indicates its infectious and also its communicable nature, but thus far single rather than multiple cases have been observed in family and other intimate groups of persons. However, two cases in a family have very rarely been noted, and in one instance an institutional outbreak has been reported in which among 21 inmates of a girls' home 12 cases arose, with 5 deaths.[8] Whether more accurate means of diagnosis through which the non-localizing or "abortive" and the frankly paralytic lethargic cases would be more certainly associated would lead to a general revision of present views regarding multiple cases can only be surmised. Obviously, in the interest of knowledge as well as of the prevention of the disease, close attention to this point is desired.

It is now a matter of great importance to determine the precise nature or etiology of lethargic encephalitis. Many unsuccessful attempts have been made to communicate the disease to monkeys and other animals through the inoculation of nervous tissues showing the particular lesions, in the manner so readily and successfully employed in monkeys for poliomyelitis. This circumstance alone would serve to distinguish this epidemic encephalitis from epidemic poliomyelitis. But in two or three instances what are stated to be successful transmissions of the disease to animals have been reported.

Von Wiesner,[9] of Vienna, inoculated a monkey subdurally with nervous tissues from a fatal case of von Economo's. This animal quickly became severely sick and died in about forty-eight hours. At autopsy a meningo-encephalitis was found, and from the lesions a diplostreptococcus was cultivated. While von Wiesner regarded this experiment as successful, further investigation has indicated that the infection with the bacteria was an accidental and secondary

process and the diplostreptococcus is not etiologically related to lethargic encephalitis.

Loewe, Hirshfeld and Strauss[10] inoculated rabbits and monkeys with filtered extracts of the nasopharynx of cases of the encephalitis, and, also, with filtered nasopharyngeal washings, and have induced a meningo-encephalitis in those animals. Apparently they did not succeed in infecting those animals by inoculating the affected nervous tissues themselves. They also believe that they have cultivated a minute organism, resembling the globoid bodies of poliomyelitis, which they think may be the inciting microbic agent of the disease. Discrepancies exist between the positive results of these authors and the many failures of others with similar inoculations which only greater experience can clear up.

Finally, McIntosh,[8] of the London Hospital, announced that a monkey inoculated with the material from the fatal cases in the Home for Girls, already alluded to, presented lethargic symptoms and tremors, and died. The brain on examination is said to have shown lesions similar to those found in human cases of lethargic encephalitis.

The foregoing account represents, in brief, the present state of our knowledge of the interesting and important disease—lethargic or epidemic encephalitis. Obviously, that knowledge is still very imperfect. It is still too soon to say whether or not we are now at the threshold of the clearing up, by way of animal experiment, of the etiology and mode of communication of this menacing disease, as was accomplished so recently, and also by animal experiment, in the case of poliomyelitis. It is to be sincerely hoped that we are. But at this moment, and while waiting for the ultimate and convincing experimental results, one need entertain no doubt of the infectious and communicable nature of lethargic encephalitis.

The belief that lethargic encephalitis is a communicable disease imposes certain responsibilities upon the medical profession to limit its spread. The outstanding obligation is perhaps the close study of suspected cases in order to determine their real nature, meanwhile holding them under such conditions of isolation as is usual with this class of diseases. Then every effort should be made to determine the existence of and to detect and control the ambulant

or abortive cases, having in mind that they may be more significant than the frankly lethargic and paralytic ones from the public health point of view. Since the nasopharyngeal secretions have become suspect as harboring the inciting microbic agent, adequate measures of controlling the distribution of those secretions into the surroundings of patients should be carried out. It is self-evident that the physician should invite the coöperation of pathologist and bacteriologist in attacking the unsolved problems presented by this unusual disease. It is to be hoped, indeed, that the disease may not secure a permanent lodgment in the country, but upon a wider knowledge of its occurrence and a deeper understanding of its nature, which the studies of the immediate future may yield, much may depend.

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PROLONGATION OF THE "S–T" INTERVAL OF THE VENTRICULAR COMPLEX AS SHOWN BY THE ELECTROCARDIOGRAPH

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The study of electrocardiograms has advanced to a conspicuous degree the recognition of lesions of the heart. At the present time the interpretation of abnormal ventricular complexes is receiving considerable attention, and any observations which may bear on this question give sufficient excuse for their being recorded.

The normal ventricular complex has certain definite characteristics which, on the whole, fall within narrow limits. The main points in which deviation from the normal may occur are in the time occupied by the various parts of the ventricular complex and in the form of the deflections constituting this complex. For the sake of convenience the ventricular complex may be divided into two main segments, namely, the *Q–R–S* period and the *S–T* period. The *Q–R–S* period includes the primary deflections, starting at the beginning of *Q* and finishing at the end of *S*. The *S–T* period commences at the end of *S* and terminates at the end of *T*. The sharp spike-like deflections of the *Q–R–S* period in the normal electrocardiogram are too well known to necessitate repeated description. The normal *T* deflection is less constant in its form, and as yet little is definitely known concerning deviations of this spike. The time relations of these two periods are definitely known. In the normal electrocardiogram the *Q–R–S* period never exceeds 0.1 second while the *S–T* period should not exceed 0.28 second. Thus the total *Q–T* interval in the normal electrocardiogram does not exceed 0.38 second. Although as yet the exact meaning of the *T* deflection is

not definitely decided, it has been demonstrated that the termination of this wave coincides with the beginning of the second heart sound. Therefore it may be presumed that it represents the termination of the ventricular systole.

Animal experiments[1] [2] have demonstrated that lesions of either the right or left branches of the bundle of His produce definite changes both in the form of the ventricular complex and in the duration of its various parts. Carter[3] has reported a series of cases showing changes in the ventricular complex analogous to those obtained by animal experiments, and concludes that these are the result of lesions of one or other branches of the bundle of His. He lays down the principles that lesions of this character give the following changes in the ventricular complex:

(*a*) *Q–R–S* interval exceeds 0.1 second, and, as a rule, constitutes more than one-third of the entire complex.

(*b*) Relative increased amplitude of initial deflections.

(*c*) Final deflection *T* usually in a direction opposite to that of the prominent initial deflection. May be upright or inverted.

(*d*) Initial deflections almost always show notching in one lead at least. Many bizarre forms seen.

(*e*) Final deflection *T* frequently much exaggerated.

These points form the basis for determining the gross lesions of the branches of the bundle of His. In a more recent communication the same writer[4] deals extensively with the pathological findings in such cases not only in regard to the main branches of the bundle of His but also in regard to the terminal arborizations. Oppenheimer and Rothschild[5] report a series of similar cases, with 14 autopsies, in 13 of which there was present diffuse disseminated patchy sclerosis which was more marked in the left ventricle than in the right. Another important point brought out in their communication was the frequency of closure of the anterior descending branch of the coronary artery. This occurred in 8 of the 14 cases, and in 4 others there was pronounced diffuse coronary sclerosis.

[1] Eppinger and Rothburger: Ztschr. f. klin. Med., 1910, lxx, 1.
[2] Lewis and Rothchild: Phil. Tr. Roy. Soc., series B, ccvi, 181.
[3] Arch. Int. Med., 1914, xiii, 803.
[4] Carter: Arch. Int. Med., 1918, xxii, 331.
[5] Jour. Am. Med. Assn., 1917, lxix, 429.

Robinson[1] has reported a series of cases demonstrating various degrees of abnormal ventricular complexes under diverse conditions. Some of these cases show ventricular complexes which are practically identical with those of lesions of the branches of the bundle of His, while others are not so conspicuously aberrant. The same author has also drawn attention to the frequent temporary character of this condition, indicating that there is not necessarily a definite structural change present. That minor changes in the ventricular complex may indicate abnormal conditions in the ventricle has been demonstrated by Neuhof[2] in regard to the increased width of the *R* deflections, which sign he concludes is the result of myocardial degeneration.

Up to the present attention has been chiefly directed to the prolongation of the *Q–R–S* period. But there is another abnormality of the ventricular complex which has received as yet little or no attention, namely, the prolongation of the *S–T* interval, and it is with this condition that the present communication is concerned chiefly.

Prolongation of the S–T Interval. In Table I a number of cases are outlined which exhibit prolongation of the *S–T* interval without prolongation of the *Q–R–S* deflections. On analyzing these cases certain points of importance are evident:

1. *Transverse Cardiac Dulness.* Although percussion is considered by some very competent observers to be a notoriously unreliable method of obtaining accurate data as to the size of the heart, it may be taken at least as a rough guide. In these cases the almost uniform enlargment of the cardiac dulness is most conspicuous. In only 4 cases in this measurement less than 15 cm. In one of these, a child of 13 (Case 26), a transverse cardiac dulness of 14 cm. is most abnormal, and it may be presumed in this case there is distinct evidence that the heart was enlarged. In the other three cases percussion does not give conclusive proof of this condition. With these exceptions the physical examinations of all these patients would afford reason to believe that cardiac enlargement was the rule.

2. *Left-sided Preponderance.* The exhaustive work by Lewis and Cotton on cardiac hypertrophy and the electrocardiographic evi-

[1] Arch. Int. Med., 1916, xviii, 830. [2] Ibid., 1918, xxii, 45.

dence of the relative preponderance of one side of the heart over the other affords data for determining this condition. In these cases there was evidence of preponderance of the left side of the heart in all but two of the cases. In both of these the *R* spike was the principal initial deflection. Although the electrocardiographic evidence was wanting, other considerations would lead one to suppose that cardiac hypertrophy did exist, and to a conspicuous degree. The cases which do not show typical ventricular complexes of left preponderance revealed, however, distinct enlargment of the cardiac dulness. On the other hand the three instances in whom the cardiac dulness was not conspicuously increased there were typical ventricular complexes indicative of left preponderance. The almost uniform occurrance of electrographic signs of left preponderance, coupled with the evidence of increase of the cardiac dulness, affords strong presumptive evidence that cardiac hypertrophy existed in all these cases.

3. *Blood-pressure.* Assuming that cardiac hypertrophy existed in these cases it becomes necessary to account for such hypertrophy if possible. On investigating the systolic blood-pressure[1] it is found there is a pronounced elevation in 18 of the 26 cases. In all of these cases there was abundant evidence to indicate that this condition had existed for a considerable period. Furthermore, the cardiac diagnoses lend support to this view. All of these cases gave abundant evidence of chronic cardiovascular disease, although in many cases the signs were much greater than the symptoms would lead one to suppose.

In the majority of those cases with a normal or low systolic blood-pressure, other and sufficient reasons were usually present to account for the cardiac hypertrophy. Cases 14 and 26 were children with pronounced evidence of chronic rheumatic endocarditis. Case 6 was suffering from a severe septic condition, from which he eventually died. The history in this case was very suggestive of previous hypertension. In Cases 15, 19 and 20 there was evidence of extensive lesions of the aortic valves or the aorta, while in Cases 12 and 25 it was quite apparent that extensive myocardial changes had been

[1] The diastolic blood-pressure was not always recorded, it has therefore been omitted, although it was uniformly increased in proportion to the systolic pressure.

TABLE I

Case No.	Elect. No.	Age.	Cardiac diagnosis.	Trans. dulness, cm.	Rate.	Sys. B. P.	P–R sec.	Q–R–S sec.	S–T sec.	Direction of T to initial waves.	Preponderance.	Remarks
1	570	49	Hypertension	15	88	230	0.22	0.09	0.35	Same	Left	
2	46	66	Myocarditis	13	95	190	0.16	0.10	0.32	Same	Left	
3	112	58	Cardiorenal disease, anginal symptoms	20	100	180	0.20	0.10	0.32	Same	Left	
4	307	15	Multiple endocarditis	16	86	120	0.20	0.08	0.34	Same	Left	X
5	288	58	Myocarditis anginal symptoms	15	60	180	0.20	0.10	0.37	Same	Left	
	316				58		0.19	0.09	0.33	Same	Left	
6	317	69	Arteriosclerosis	18	68	140	0.19	0.08	0.31	Same	Left	X died of empyema
7	156	40	Cardiorenal disease, anginal symptoms	16	67	210	0.21	0.09	0.32	Same	Left	
8	332	67	Myocarditis anginal symptoms	20	60	170	0.18	0.08	0.34	Same	Left	
9	350	35	Mitral endocarditis, anginal symptoms	21	67	195	0.18	0.10	0.31	Same	Left	
10	231	55	Myocarditis anginal symptoms	15	75	200	0.16	0.09	0.31	Same	Left	
11	151	70	Myocarditis anginal symptoms	12	51	160	0.20	0.09	0.35	Same	Left	
12	110	63	Myocarditis anginal symptoms	18	60	130	0.18	0.08	0.34	Same	Left	X
13	42	70	Myocarditis anginal symptoms	19	75	210	0.18	0.08	0.38	Same	Left	
14	328	50	Aortic disease, anginal symptoms	19	75	180	0.17	0.09	0.32	Same	Left	
15	41	67	Aneurysm anginal symptoms	13	65	140	0.20	0.08	0.32	Same	Left	X
16	312	60	Heart-block, myocarditis	18	40	198	....	0.09	0.40	Same	Left	
	312a				43	195	0.2	0.09	0.40	Same	Left	
17	4		Arteriosclerosis myocarditis		43	180	0.4	0.16	0.54	Same		
	19	70		16	75	190	0.21	0.13	0.36	Same		
	23				100	185	0.18	0.10	0.34	Same		
18	550	77	Cardiorenal disease, anginal symptoms	20	75	185	0.12	0.09	0.35	Opposite	Left	
19	596	38	Aortic valvular disease, anginal symptoms	21	70	140	0.18	0.09	0.32	Opposite	Left	X
20	409	54	Aortic valvular disease, anginal symptoms	23	86	154	0.16	0.09	0.32	Opposite	Left	X
21	477	47	Cardiorenal disease, anginal symptoms	24	70	230	0.20	0.10	0.32	Opposite	Left	
22	395	58	Aneurysm	16	100	230	0.18	0.10	0.34	Opposite		
23	561	71	Auricular fibrillation	21	75	200?	....	0.10	0.32	Opposite	Left	
24	114	63	Auricular fibrillation, anginal symptoms	21	64	185?	....	0.09	0.32	Opposite	Left	
25	394	45	Auricular fibrillation and heart-block	17	31	120?	....	0.08	0.46	Opposite	Left	X
26	429	13	Multiple endocartitis	14	67	85	0.19	0.09	0.35	Same	Left	X

occurring for many years. The evidence in favor of pronounced cardiac hypertrophy is almost uniformly present in these cases.

4. *Cardiac Rate.* Slow cardiac rate is common in these cases. But the length of the *S–T* period is not constantly in proportion to the rate of the cardiac rhythm. There may be a progressive increase in the pulse-rate, with an associated diminution in the *S–T* interval, until this reaches a more or less constant duration, and there may be a slight increase of the prolongation, with slowing of the cardiac rate. But a variation in the length of the *S–T* interval without a proportionately conspicuous change in the rate of the cardiac rhythm occurs with fair frequency. Certain cases also show a parallel decrease in the *P–R* and *Q–R–S* intervals along with the decrease in the *S–T* intervals. This would lead one to suppose that this decrease was dependent upon an improvement in the function of the cardiac conduction system, which is comparable to the findings of Robinson in reference to the temporary character on occasion of bundle branch lesions.

Cases 5 and 17, in Table I, also conform to this general improvement in conduction, which is also coincident with an increase of the cardiac rate. On the other hand, in spite of an increase in the rate to normal, the *S–T* interval and to a less extent the *P–R* and the *Q–R–S* intervals do not completely return to the normal time limits.

Many of the cases in Table I show a normal cardiac rate, but still there is a pronounced increase in the *S–T* interval as shown particularly in Cases 1, 8, 11, 12, 13, 18, 22 and 26. If the prolongation of the *S–T* interval were altogether due to slow cardiac rhythm it would be expected that after long diastolic periods the *S–T* interval would be greater than after short diastolic periods. This is found not to be so. In a case in which there were diastolic periods of great length amounting to twenty seconds the *S–T* interval of the ventricular complexes following such long diastolic periods averaged 0.56 seconds, while the *S–T* intervals during comparatively rapid periods of the heart's action averaged 0.55 second.

It is reasonable to suppose therefore that prolongation of the *S–T* interval is not altogether due to slow cardiac rhythm, although this may exert a certain influence.

Cause of Prolongation of the S–T Interval. The *Q–R–S* deflections are now accepted as being representative of the excitation wave passing through the main bundle of His, its main branches and their arborization. The work of Lewis and Rothschild has gone far to prove this theory. They bring forward evidence to prove that the length of time it takes for the excitation wave to appear on the surface of the heart depends upon two factors, namely, the length of the Purkinje tract and the thickness of the ventricular wall. In the cases here reported it will be noted that the *Q–R–S* interval is either grossly prolonged or is in the upper limits of normality, but yet the configuration of the ventricular complexes show little or no change from the normal, except in so far as the signs of left-sided preponderance are concerned. This prolongation of the *Q–R–S* interval in cases of left hypertrophy confirms a similar observation made by Lewis. This he attributed to the increased thickness of the left ventricular muscle. In certain cases this is not an adequate explanation, as the rapid changes in the length of this period could hardly be dependent upon like changes in the thickness of the ventricular.

Lewis makes the statement that "the length of the initial phases of the bigram may be taken to indicate the duration of the process of activation." Delay of this process of activation may be produced either by injury to one or other branches of bundle division or by a generally lowered power of conductivity on the part of the conducting system as a whole.

The exact interpretation of the *T* deflection is not at present settled, but Lewis considers that it is indicative of the decline of the excitatory process. If this be the case it would indicate that this is considerably retarded in the cases cited above. There is not enough evidence at hand at the present time to determine this question positively. However, the fact remains that there is a distinct prolongation of the ventricular systole which mainly occurs after the wave of activation has been completed. It would appear probable that this were due in part to the increased volume of the muscle, particularly, as it has been shown that this has a distinct influence on the length of the activation wave as shown by the lengthening of the initial deflection.

It is well known that when a muscle is fatigued the contraction time becomes distinctly slower. The heart is all these cases was laboring under a greatly increased burden and was performing the work in a comparatively satisfactory manner. It must be considered to what an extent the prolongation of the ventricular systole (*S–T* interval) is a compensatory phenomena the result of muscle fatigue.

The question of fatigue is associated so intimately with nutrition that it was considered probable that some clue to the role played by muscle fatigue in producing prolongation of the *S–T* interval might be found in cases of malnutrition. Such cases were not at hand, but it was observed that in cases of diabetes during periods of prolonged starvation, or during a very low calory diet, that the *S–T* interval was distinctly delayed. It was found, further, that when the diet was increased the *S–T* interval approached the normal, although it did not necessarily completely return within the normal limits. (See Table II.) Also it was observed repeatedly that on rest the prolongation of the *S–T* interval tended to diminish, although in other respects there was little or no change in the patient's condition except for a striking relief from the precordial distress.

There were recorded in 65 per cent. of the cases, symptoms which for want of a better term have been classified as "anginal." These were usually characterized by precordial oppression or pain, sometimes radiating to the neck or the left arm. The acute paroxysms of "angina pectoris" were not frequent, although a history of such was sometimes obtained. There was described also a sensation of intense exhaustion. The question arises whether there is an association between the prolongation of the ventricular systole and these symptoms. It is an accepted physiological fact that the greater the resistance opposed to the contractile phase of muscular activity the greater the degree of tension in the muscle. These symptoms usually occurred in cases with an increased systolic blood-pressure or in those showing conspicuous damage to the aortic valves or aorta. Under these circumstances the muscular load would be greatly increased, and, as a result, the muscular tension likewise. Cases which complain of intense paroxysms of precordial

TABLE II.

Case No.	Elect. No.	Age.	Diagnosis.	Trans. dulness, cm.	Rate.	Sys. B. P.	P–R sec.	Q–R–S sec.	S–T sec.	Direction of T to initial wave.	Preponderance.	Diet.
1	268 284	28	Diabetes	11	73 75	99	0.18 0.18	0.06 0.06	0.39 0.32	Same Same	None None	Five days' starvation; full diet.
2	536 555	36	Diabetes	13	60 64	110	0.16 0.16	0.07 0.07	0.35 0.30	Same Same	Left	One days' starvation; three days, 10 gm. H., full diet.
3	559 552	29	Diabetes	....	83 88	115	0.16 0.16	0.08 0.08	0.32 0.28	Same Same	Left slight, none	Moderate diet; low fat; full diet.
4	540 553	26	Diabetes	12	70 75	118	0.17 0.17	0.08 0.08	0.32 0.29	Same Same	Left slight, none	Moderate diet; low fat; full diet.
5	535	52	Diabetes	13	92	125	0.15	0.08	0.32	Same	Left	One days' starvation; three days, 10 gm. C. H.
6	537	22	Diabetes	10	70	90	0.17	0.08	0.32	Same	None	One day, 64 gm.; one day, 30 gm. C. H.
7	538	23	Diabetes	11	66	105	0.16	0.07	0.32	Same	None	Full diet; starved three days previously.
8	575	67	Diabetes	13	83	120	0.16	0.06	0.30	Same	None	Moderate diet.
9	576	5	Diabetes	9	75	80	0.16	0.06	0.29	Same	None	Low diet; no fats.
10	577	69	Diabetes	13	72	70	0.13	0.09	0.32	Same	Left	Moderate diet.

pain do not, as a rule, show lengthening of the *S–T* interval, which is suggestive that prolongation of the ventricular systole may be a beneficial phenomena in these cases, and that when it does not occur cardiac spasm may result from increased work.

Prognosis. The prognosis in these cases has been remarkably good, in spite of a cardiac condition which frequently gave rise to considerable apprehension. As yet it has been impossible to complete statistics comparing the probable morbidity and mortality of these cases with similar ones without prolongation of the *S–T* interval. The fact that none of these cases have died from cardiac failure, while many of them have been under observation for some years, leads one tentatively to consider this condition with favor.

Conclusions. 1. Prolongation of the whole ventricular systole may occur without definite evidence of localized injury to the bundle of His or its branches.

2. Prolongation of the *Q–R–S* interval occurs with left-sided hypertrophy.

3. Prolongation of the *S–T* interval may occur with or without lengthening of the *Q–R–S* period and is intimately associated with left-sided ventricular preponderance and precordial pain.

4. Similar prolongation of the *S–T* interval may occur in diabetes, particularly when the individual is on a very low calory diet.

STUDIES ON MALARIA CONTROL[1]

I. THE RELATIVE FREQUENCY OF MALARIA IN PERSONS OF DIFFERENT AGES AND AGE GROUPS IN A LARGE AREA OF GREAT PREVALENCE

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The observations to be presented here are based upon a survey made during 1916 and 1917 of all persons of all ages living in an area of 328 square miles in Bolivar County, Mississippi. This is in the heart of the Mississippi Delta and is one of the most intense malarial sections of the United States. A careful history as to whether attacks of malaria had occurred during the past twelve months was obtained and blood was collected and examined by the thick film method from 31,459 persons living in this area. All ages and classes of people were examined alike, and therefore it is believed that the results obtained are conclusive so far as that particular locality is concerned.

Of the total number of 31,459 persons, 40.3 per cent. gave a history of having had one or more attacks of malaria during the previous twelve months and 28.96 per cent. of these were found positive by blood examination. Examination of the blood of those who gave negative histories showed that 15.93 per cent. of them had malaria parasites in their blood. If we add those who gave negative histories, but who were found positive upon blood examination, to those who gave definite history of attacks during the previous twelve months we have an indicated prevalence of malaria during the year of at least 49.81 per cent. This includes the entire

[1] This is one of a series of papers to be published, based largely or entirely upon malaria control work conducted jointly by the International Health Board and the Mississippi State Board of Health.

population and shows that the observations were made in an area in which malaria is very prevalent.

Table I shows in detail the percentage of infection found in people of different ages and age groups. It will be noted that the height of the infection is reached at the age of six and that the five-year group showing the heaviest infection is the five- to nine-year-old group. The percentage of infection of persons under twenty years of age is 23.56 per cent. against 19.22 per cent. for persons over twenty years of age.

The blood index by five-, ten-, twenty- or thirty-year age groups is shown graphically in Chart I[1].

The blood index by years up to twenty is shown graphically in Chart II.

The population of the area studied averages 90 per square mile, consisting of 17.8 per cent. whites and 82.2 per cent. negroes. The negroes were found to have 36.61 per cent. more infection than whites. This is shown in contrast, and graphically in Charts III and IV.

Chart V shows graphically the history index by age groups. This is based upon the history of one or more attacks during the previous twelve months. It is seen that malaria is considerably more prevalent in children than in adults.

The distribution of the total amount of malaria in people of different ages and age groups shows that approximately 50 per cent. of all the malaria in the country occurs in persons under twenty years of age. Approximately 15 per cent. of all the malaria falls in the age group from five to nine inclusive. Chart VI shows graphically the distribution of all the malaria of the country by five-year-age groups.

SUMMARY. 1. In an area of 328 square miles in Bolivar County, Mississippi, during 1916 and 1917, blood examination of all people living in this area showed that malarial parasites are present in 23.56 per cent. of persons under twenty years of age as compared with 19.22 per cent. of persons over twenty years of age.

2. The highest five-year period is from five to nine inclusive.

3. Negroes were found to have 36.61 per cent. more infection than whites, and the high point is reached with negro children much earlier than with white children. (See Chart IV.)

[1] The charts will appear elsewhere.

4. Approximately 50 per cent. of all the malaria in the locality investigated was found in persons under twenty years of age.

This table shows the percentage of all persons of certain ages and age groups found infected upon first examination.

Age in years.	Percentage infected.	Age.	Percentage infected.
Under 1	16.61	15	23.85
1	16.18	16	23.75
2	20.54	17	24.60
3	21.58	18	22.97
4	24.40	19	24.15
Under 5	20.18	15 to 19	23.82
5	24.27	Under 20	23.56
6	27.13	20 to 24	21.24
7	25.35	25 to 29	20.99
8	24.70	30 to 39	18.64
9	25.27	40 to 49	19.96
5 to 9	25.32	50 to 69	18.61
Under 10	22.88	70 to 99	18.25
10	25.00	100	16.67
11	26.79	Adults, age not given	17.01
12	22.01	Over 20	19.22
13	24.56	All	21.18
14	25.87		
10 to 14	24.74		

A CASE OF AYERZA'S DISEASE: CHRONIC CYANOSIS, DYSPNEA AND ERYTHREMIA, ASSOCIATED WITH SYPHILITIC ARTERIOSCLEROSIS OF THE PULMONARY ARTERIES

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The discovery by Vaquez, in 1892, of the syndrome of chronic cyanosis, persistent polycythemia, and enlargement of liver and spleen, in the absence of organic heart involvement; and Osler's service later in calling the attention of the medical profession to this new complex, established a definite place for it in nosology as Vaquez's disease, Osler's disease, Osler-Vaquez disease, erythremia, primary polycythemia, splenomegalic polycythemia, polycythemia with chronic cyanosis, myelopathic polycythemia, cryptogenic polycythemia, erythrocytosis megalosplenica, etc. Lucas[1] collected 149 undoubted cases and 30 questionable ones from the literature. Since his paper the number of reported cases has increased to over 200. Lucas, in his summary of the reported cases, came to the conclusion, that in the light of the present knowledge of the disease, it was difficult to establish a hard and fast line between cases of polycythemia, probably secondary in form but of obscure origin, on the one hand, and unquestionable cases of primary polycythemia or erythremia, on the other. The reported autopsies, twenty-three in number, had thrown but little light on this question.

Since Lucas' paper the question as to the primary or secondary nature of the Osler-Vaquez syndrome has received more attention, and there is an increasing number of cases in which the syndrome

[1] Arch. Int. Med., 1912, x, 597.

has been found associated with other conditions in such a way as to make it certain that the symptom-complex was purely secondary. The separation of a primary polycythemia from a secondary erythrocytosis has become more difficult; and the question may well be asked, if a primary Osler-Vaquez disease exists. The uncertainty attending this question has led recent writers to split up the Osler-Vaquez disease into a number of groups. The fact that cases are reported under such titles as "Polycythemia without Splenomegaly," "Polycythemia without Cyanosis," the "frustrate form," "congenital form," "cardiac form," "Geisbock's disease," "Blumenthal's disease," etc., reveals the confusion attending the effort to fix the symptom-complex as a distinct morbid entity. Similarly the attempts to separate forms upon a basis of the number of red cells, state of the bone-marrow, etc., are evidence of the difficulty in giving the syndrome a fixed position in nosology.

Does a primary erythremia exist? The writer believes not, certainly not in cases showing chronic cyanosis and dyspnea. Why should a case of pure or absolute polyglobulism have either cyanosis or dyspnea? On the other hand there is every reason why a case of chronic cyanosis and dyspnea should develop a chronic erythremia. It is most probable, in the writer's opinion, that all erythremias associated with cyanosis and dyspnea (with a theoretical exception of neoplastic overformation of red cells, yet to be definitely shown to exist) are *compensatory* in nature.

With this point stated, the writer presents a unique case of Osler-Vaquez disease, which was under clinical observation for five years, with full autopsy and microscopic findings, in which the Vaquez syndrome of chronic cyanosis, persistent high erythremia, enlargement of liver and spleen, and hyperplasia of bone-marrow, are shown to be secondary to syphilitic disease of the pulmonary arteries ("Ayerza's disease").

HISTORY OF THE CASE

Mr. L. H., American, aged about forty-three years, laborer, was admitted to the medical clinic (Dr. George Dock) of the University Hospital, Ann Arbor, January 17, 1907, and was presented in the clinic on the following day. His chief complaints at that time were *difficult breathing, palpitation,*

blueness of skin and lips, general weakness, dropsy and frontal and occipital headaches.

His family history, so far as known to him, was negative. His father was living; his mother had recently had an amputation of the right tibia for thyroid metastasis. He was unmarried. He denied venereal disease and claimed to drink and smoke but rarely. His health had been good up to about thirty years of age, when he began to have asthmatic attacks at night. These increased in severity and frequency. At thirty-six years he had a sudden attack of apnea and was unconscious for several minutes. From this time on he began to have more frequent and severe asthmatic attacks, at irregular intervals, usually at night. Four years before entrance to the hospital he first noticed blueness and swelling of his face, hands and feet. He was told by a physician that he had "heart trouble," and under medical treatment his symptoms improved and the cyanosis disappeared and did not return until September, 1906. From this time on attacks of cyanosis, palpitation and dyspnea became more frequent and severe, with severe frontal headaches, frequent dizziness, prominence of eyes and feeling of thoracic constriction, particularly when lying down. Pressure upon the sternum produced a sensation of "smothering." He had no dysphagia and no marked gastro-intestinal disturbances.

Physical examinations by Drs. Dock and Smithies showed a man of medium build, with thin panniculus, and marked cyanosis over face and neck; hands and feet were moderately blue; color deepened when patient stood or let his arms hang down. When lying down his face and neck became slaty blue, the cyanosis decreasing after several moments. Exercise and excitement increased the cyanosis. Palate and tongue were deep purple; eyes prominent, especially the right. Conjunctivæ suffused, especially on right. The pupils were of moderate size, equal and active. The external jugulars were prominent, dilated and filled from above. There was moderate pulsation of the carotids. The thyroid was negative; no tracheal tug. Over the trunk the skin had a bluish cast. The thorax moved *en cuirasse;* respirations were shallow, not increased when resting, but rapidly increasing on slight exertion. Heart-beat faintly seen in fifth intercostal space, inside the nipple. Heart-rate not increased. No arrhythmia. Palpation of lungs negative. Percussion showed good resonance over lungs, low liver dulness, an abnormal area of dulness beneath the upper portion of the sternum and an atypically situated precordial outline. Splenic dulness barely made out to edge of ribs. Auscultation of lungs showed diminished vesicular over entire right side above fifth rib; below this inspiration was sharp and blowing, expiration soft and prolonged, with a few piping rales. On the left side there was bronchovesicular breathing to the second rib, with increased vesicular below, with more numerous rales. Spoken and whispered voice were negative.

Auscultation of heart revealed faint sounds heard with difficulty. The

first sound at apex was soft and impure; the pulmonic second moderately accentuated. Over base of heart, sounds could barely be heard.

The radial pulse was slow, moderately full, fuller on left than on right. Radial arteries moderately sclerotic. The blood-pressure varied on the two sides; on the left systolic was 156 mm. Hg., diastolic 109 mm.; on the right the systolic was 146, the diastolic 98 mm. (Erlanger apparatus, 12 cm. cuff).

The abdomen was somewhat distended in region of umbilicus. Lower border of liver dulness low. The liver was felt with difficulty at the end of inspiration. Splenic dulness to edge of ribs. Spleen was not palpable. No palpable mass in abdomen. Lymph nodes not enlarged.

Ophthalmologist's (Dr. W. H. Parker) examination of eyes showed a moderate conjunctival injection; marked venous congestion of retina, with edema of macular region. No hemorrhages.

The left nasal fossa was found to be partly occluded. Examination of larynx negative.

When presented in the medical clinic, January 18, 1907, the red blood cell count was found to be 6,450,000, white cells 6500 and hemoglobin 100 per cent. The blood was deep red in color, flowed slowly. The red cells were normal in appearance; no nucleated forms were seen and the differential white count was negative. Urine contained a moderate amount of albumin and many small granular casts and cylindroids.

A tentative diagnosis of "Osler-Vaquez disease" was made by Dr. Dock at this time.

Later fluoroscopic examination showed a vaguely outlined, diffuse, non-pulsating shadow above the heart, especially dense about the root of the lungs and great vessels, extending up into the neck. Heart downward and inward. Diaphragm low on both sides, especially so on right side.

A radiogram confirmed the fluoroscopic findings: A mass almost as dense as the heart filling in the mediastinum. No definite lines of pulsation can be seen. Tumor appears to occupy both mediastinal spaces, lying in close approximation to heart, lungs and adnexa. Points of greater or less opacity can be seen throughout the lungs, the infiltration being more marked on the left than on the right.

Course of Disease. The patient at first improved somewhat under treatment, was able to go about the hospital, his cyanosis, erythremia and dyspnea varying in degree with conditions. About three months after entrance, while walking in the hall, had a sudden sense of pressure in upper thorax, felt as if he were being choked, could not breathe or speak, fell to the floor and became unconscious. When placed in bed was cyanotic and markedly dyspneic and complained of pains in the thorax. Respiratory sounds were very weak, with numerous piping rales; heart sounds very weak, rate 129; systolic pressure 106, diastolic 55.

This attack was followed by a period of increasingly frequent attacks of extreme cyanosis, with more or less pronounced erythremia, marked

dyspnea, associated with unconsciousness, headaches, gastro-intestinal pain and albuminuria. He was constantly cyanotic, but during the two years he was in the hospital had about seventeen attacks of extreme cyanosis ("black"), with extreme dyspnea, feeling of suffocation, precordial distress and palpitation, these attacks lasting for a few minutes or for several hours. During the attacks the heart rate was accelerated, going from 60 to 130. The peripheral vessels were injected, but there were no positive venous pulsations. During the attacks there was almost complete absence of breath sounds, with few high-pitched musical rales. Heart sound became very faint. The eye-grounds always showed extreme engorgement and edema. There was no bleeding, except occasionally from the nose. Enlargement of the spleen was first positively determined October 21, 1907, when it could be palpated below the edge of the ribs.

The *erythremia*, which had been noted on entrance, persisted, varying greatly, usually in proportion to the severity of the attacks of cyanosis. In over one hundred blood counts taken during the 605 days in hospital the red blood cell count only twice fell below 6,000,000, the lowest count being 5,040,000 on March 25, 1907, and the highest 9,500,000 on May 8, 1908. The average of these counts was over 8,000,000 per c.mm. Blood taken from different parts of the body showed some variation in the number of red cells. The hemoglobin was always above 100 per cent., frequently as high as 156 per cent. (Miescher); with prolonged paroxysms of cyanosis and red blood cell counts of 8,000,000 per c.mm., the average hemoglobin reading was 132 per cent. The white cell count ran within normal limits, 6000 to 10,000 and the differential white count showed little variation; at times a slight increase in eosinophiles and lymphocytes, and occasionally a few myelocytes after one of the acute attacks. Nucleated reds were occasionally noted. With the red cell count at 7,400,000 the specific gravity of the blood was estimated at 1062. The coagulation time was shortened; the viscosity increased.

The patient remained in the hospital 605 days, being discharged September 12, 1908. At the time of discharge he was still showing an increase in the severity of his attacks of cyanosis, dyspnea, headaches, visual disturbances (diplopia, "turning black"), gastro-intestinal symptoms (loss of appetite, intense paroxysmal pains in epigastrium radiating to lower abdomen, constipation alternating with diarrhea). His albuminuria had increased. Stools were negative. He had no dysphagia or vomiting. Temperature was never raised. The last radiograms seemed to show a gradual extension of the mediastinal mass.

Dr. Dock inclined to a diagnosis of Osler-Vaquez disease, with albuminuria and chronic pericarditis; Dr. Smithies to a diagnosis of polycythemia, with mediastinal tumor. The case was reported by the latter, as Case I, in an article on "Clinical Aspects of Tumors of the Mediastinum."[1] In this

[1] Jour. Am. Med. Assn., 1908, li, 897.

article, Dr. Smithies summarized the case as follows: "The case presents many of the findings of the condition of chronic cyanosis with erythremia described by Vaquez, Osler and others. The spleen, however, is not enlarged and the mediastinal tumor appears to be a discoverable cause for the symptoms, which is unusual or not yet reported for cases of true cyanotic polycythemia, Vaquez-Osler malady. It is not quite determined that the two conditions do not exist, but in view of the rather marked variations in the cyanosis and the red cell count, it is probable that much of the polycythemia is due to extensive pressure in the thorax on the great vessels. The changes in spleen and bone-marrow might come on later and give a characteristic picture of erythremia vera."

After leaving the hospital in 1908 the patient became a popcorn peddler in Ann Arbor and was seen at intervals by members of the clinic of internal medicine. He was still subject to attacks of cyanosis and dyspnea, but was for some time more comfortable than he had been during the previous two years. He was able to work at his popcorn business about half the time.

On April 28, 1910, his blood count was again made in the clinic of internal medicine (Dr. A. W. Hewlett). The red cell count was 7,200,000, white cells 10,500 and hemoglobin 120 per cent. He was first examined by Dr. Hewlett on the next day. He found his heart enormously dilated and the lower portion of the chest retracted and immobile. Abdomen was prominent, but there was no ascites. Spleen was just palpable. Lungs showed signs of emphysema, but little bronchitis. Legs were moderately edematous. The spectroscopic examination of his fresh blood, which was dark and thick, gave the characteristic band of oxyhemoglobin. Urine showed trace of albumin and few granular casts. He appeared at intervals for examination and advice, his condition remaining about the same.

In the *Transactions of the American Ophthalmological Society* for 1910 his case was again reported, this time from an ophthalmological standpoint, by Drs. Parker and Slocum, of the University clinic of ophthalmology.

By this time the diagnosis of a mediastinal tumor had been completely abandoned and the case was regarded as an uncomplicated one of chronic cyanosis with polycythemia (Osler-Vaquez disease). Parker and Slocum give in their article (Case I) a detailed description of the retinal appearance of intense engorgement and edema. They noted the presence of a small venous aneurysm, which later was found to have ruptured. A second retinal hemorrhage was also seen.

When patient was seen December 2, 1910, his cyanosis was greatly increased; his hands were black.

He was seen again, on January 31, 1911, by Dr. Hewlett, who found the spleen fairly easily palpable and "purpuric" spots about his joints and over his legs, some as large as a dime, and elevated. During the winter he had a very severe attack and vomited black particles.

He was readmitted to the hospital on October 24, 1911, his condition

having become such that he was obliged to give up work. At this time he gave his age as fifty-two years. His chief complaint was still dyspnea, weakness and cyanosis. He still denied venereal disease and alcoholism. His symptoms were about the same as when last seen. He had not lost weight; had had no blood in stools or sputum. Vision is blurred at times; and has headaches, accompanied by dizziness and nausea. Sleeps poorly. Has no thoracic pain.

The physical examination at this time (Drs. Hewlett and Van Zwaluwenburg) showed less cyanosis than in previous admissions. Had firm, hard edema over thighs and legs, not much over back; face was puffy. Conjunctival vessels were enormously engorged; many venules were blue black. Veins of neck were still full until the patient was almost upright; they collapsed when he was upright. Thorax moved poorly; there was inspiratory retraction all the way round at level of diaphragm. Abdomen was very full flat above and bulging in the flanks. Abdominal breathing marked. Percussion showed an enormously enlarged heart. Liver was a handbreath below the level of the ribs, reaching nearly to navel and confluent on left with splenic dulness. The lungs were nowhere very resonant; the lower borders moved slightly, but symmetrically. There were no localized areas of diminished resonance over front or back. Tactile fremitus was negative. Breath sounds all over the lungs were feebly vesicular, almost inaudible over bases and back. Numerous crackling rales were present over the upper portion, large dry ones below, somewhat more abundant on right. The whole left upper portion more silent than on right. No localized voice changes. The first sound at apex was dull and distant, almost replaced by a systolic murmur; the second sound poorly heard, although easily felt. The murmur waned and waxed to another maximum in the fifth intercostal space, about two finger-breadths to left of sternum. It was poorly transmitted to the axillæ and not heard in the back. The second sound in the tricuspid area was relatively loud. At base both sounds were distant; the valvular areas could not be accurately localized; the systolic murmur from below was only occasionally audible at base. No diastolic murmur. The radial pulse was small, soft, quick and frequent. Hands were cold and moist. The liver margin was felt as a firm semi-elastic mass, without a distinct edge. The spleen was just palpable in the anterior axillary line in the left hypochondrium, otherwise the belly was tympanitic. No fluid wave. The ophthalmological examination showed similar retinal engorgement and edema as before, only more marked.

Erythremia was variable as before, 7,200,000 to 8,760,000. The white cells ranged 7000 to 10,600, the proportionate count was almost normal, the polynuclears being slightly increased. No nucleated forms and no myelocytes were found at this time.

The patient's condition quickly grew worse, increasing dyspnea and cyanosis, with insomnia, nausea, purpura and finally bloody stools, blood-

streaked sputum, delirium, intense cyanosis ("black") and general collapse, leading to his death on November 14, 1911.

Clinical Diagnosis. Polyglobulism, emphysema, cardiac hypertrophy, and dilatation; chronic passive congestion; cardiac cirrhosis; hemorrhage from hemorrhoids; nephritis (?) (Dr. Hewlett.)

The autopsy was performed by me a few hours after death.

Autopsy Protocol (Dr. Warthin).

Male body, of medium frame, 172 cm. long; abdomen distended; umbilicus everted; broad, epigastric angle; precordium prominent. Skin of entire body markedly cyanotic; where least cyanotic, on the upper portions of body, it is yellowish blue. Hypostasis is extreme, particularly on legs. Genitals very cyanotic and slightly edematous. Numerous angiectatic warts over back, black in color. Over legs numerous circumscribed angiectatic vessels, forming blue-black spots size of pin-head to dime. No hemorrhages in skin. Skin over legs thickened and scaly. All superficial veins markedly injected. Mucous membranes intensely cyanotic. Scleræ yellowish. Musculature fair. Fair amount of panniculus. Marked edema over legs, moderate over trunk and upper portion of body. Rigor mortis present throughout. Palpation of abdomen negative. Liver and spleen could not be felt.

Head. Skullcap moderately thick, but almost as thin as paper in left temporal region. Meningeal grooves deeply eroded, particularly that of the left middle meningeal artery. Inner table shows marked erosion. In the right temporal region there is a sharp, spine-like exostosis projecting 1 cm. from the inner table. Dural tension increased. Dura adherent all over convexity, thickened and very tough. Adhesions between dura and arachnoid. Longitudinal sinus contains a small red clot; the veins opening into it have markedly thickened walls. Basal meninges thickened. Arachnoid over convexity thickened and shows hyaline patches. Pial vessels enormously distended. Pacchionian bodies extremely small. Carotids and basal vessels show no sclerosis. Cerebrum intensely congested and edematous. Ventricles moderately dilated. Choroid plexus markedly congested. Pineal gland very small. Cerebellum intensely congested and edematous. Hypophysis very small.

Spinal cord presents meningeal thickening, congestion and edema.

Main Incision. Panniculus very moist, light orange color. All blood-vessels engorged with dark, fluid blood. Muscles are light brownish red, soft and tear easily. No free gas in peritoneal cavity and only a small amount of clear fluid (150 c.c.). Omentum below umbilicus, moderately fat, its vessels congested. Lower border of liver reaches to umbilicus in median line; in right nipple line it is a handbreadth below edge of ribs. Spleen is large, its lower pole below edge of ribs. Stomach lying vertically, moderately distended with gas. An unusual, sweetish smell in abdominal cavity. Diaphragm in lower border of sixth rib on the right, in sixth intercostal space on the left.

Sternum osteoporotic, marrow, hyperplastic. No free gas in pleural cavities. Small amount of clear fluid (100 c.c.) in each cavity. Old adhesions over right apex, otherwise pleuræ are free. Lungs nearly meet in upper portion of mediastinum; their free edges show extreme emphysema. Mediastinal fat fairly abundant, very red in color. No remains of thymic tissue seen.

Heart. Heart is of enormous size, lying almost transversely; the greater part of the right heart lies to the right of the median line, the apex in sixth intercostal space half-way between nipple and anterior axillary lines. Apex is rounded, blunt, with no point. Pericardial sac greatly distended; no pericardial adhesions; fluid about 80 c.c., clear. All chambers of heart greatly dilated, the dilated right auricle making up one-third of the heart bulk. The right border of the right auricle reaches to the right parasternal line. On cutting the inferior vena cava there is a gush of very dark fluid blood containing small jelly clots. Left and right ventricles about equally dilated; both auricles extremely dilated, the right one in a remarkable degree; the muscle fibers of its wall widely separated. The enlargement of the heart is due chiefly to dilatation; when emptied of blood its measurements were 18 x 13 x 7.5 cm., its weight 790 gm. On the table the heart flattens into a soft, round disk. The subepicardial fat is increased, orange red in color. Irregular tendinous spot over anterior wall of right ventricle. Firm thrombus in right auricular appendage. Mitral orifice admits five fingers, slight roughening and thickening of proximal edges, but no organic insufficiency or stenosis. Aortic orifice barely admits thumb; flaps negative. Tricuspid orifice greatly dilated, admitting whole hand, flaps negative. Pulmonary orifice admits three fingers, two and a half times as large as the aortic opening. Calcareous placque in wall of pulmonary conus. Pulmonary artery enormously dilated; its wall markedly thickened, and its intima showing a condition of advanced atherosclerosis. Coronaries extremely dilated, presenting patches of sclerosis. Auriculoventricular septum intact; foramen ovale closed; no anomaly. Aorta is of medium size; its intima shows moderate sclerosis, rather linear in type, with some early atheroma.

Lungs. Right and left lungs weigh 625 and 675 gm. respectively. Both are very voluminous, with markedly emphysematous borders. Moderate anthracosis. Both show extreme congestion and edema. Airless areas alternate with emphysematous. All the branches of the pulmonary artery are markedly dilated and present an extreme condition of sclerosis and atheroma, even to the terminal branches. Lower lobes show patches of pneumonic or hemorrhagic consolidation. In the larger main branches of the pulmonary arteries the thickened intima shows porcelain-like areas, with irregular cracks and thinnings of the wall, as in syphilitic aortitis. Pulmonary veins enormously distended; their walls relatively thickened. Bronchial nodes pigmented, much congested and edematous.

Mouth and Neck Organs. Mucous membranes of mouth, pharynx, epiglottis, larynx and trachea show extreme congestion. Thyroid is small, with small amount of colloid. The parathyroids are of normal size, and very deep red. The cervical fat has the appearance of embryonic fat. Cervical lymph nodes extremely conges ted.

Spleen. Free, no adhesions. Greatly enlarged before removal; much smaller after removal and bleeding; measures then 13 x 9 x 6.5 cm., and weighs 330 gm. Firm, does not flatten on pressure. Capsule thickened, with small hyaline patches. Cut surface shagreened, deep bluish-brown red. Stroma increased; follicles not easily seen.

Adrenals. Normal in size and shape. On section show intense congestion. Medulla of right one in advanced postmortem change.

Kidneys. Left and right measure 13.5 x 8 x 5.25 and 13 x 7.5 x 4.5 cm. respectively and weigh 300 and 200 gm. They present similar appearances. Fatty capsules are abundant, reddish orange, resembling fetal fat in color and appearance. Fibrous capsules strip easily. Cortical surface smooth; deep purple red, with small areas of parenchymatous degeneration in cortex. Cortex atrophic. Cut surfaces nearly uniform in color; outlines of structure cannot be made out.

Intestines. Contain a thin soup-like, bile-stained material. No fresh blood seen. Mucosa shows extreme congestion and edema. Appendix surrounded by old adhesions. Bile passages patent. No hemorrhoids. No bleeding in rectum.

Stomach. Contains a plum-colored mucus containing some food remains. No fresh blood. Mucosa tremendously congested; chronic stasis-catarrh. Pylorus thickened, firm, slight stenosis. No erosions or ulcers.

Pancreas. Large, firm, body ends abruptly without tail. Color very dark. On section shows marked congestion; lobules large with increase of interlobular connective tissue. Vessels are dilated and show slight sclerosis.

Liver. Much enlarged, shows markings of ribs. After removal and bleeding measures 25 x 19 x 8 cm. and weighs 2000 gm. Capsule shows some thickening, particularly around ligaments. Lower border rather rounded. Consistence soft. On section bleeds freely. Marked "nutmeg liver." Vessels all greatly dilated. Stroma increased in patches beneath cortex. Gall-bladder greatly distended. Contains thin brownish fluid.

Lymph Nodes. Mesenteric and retroperitoneal lymph nodes extremely congested, edematous and very soft. Few atrophic hemolymph nodes, brown in color.

Prostate. Negative, except for intense congestion.

Testes. Marked congestion and edema.

Bone-marrow. Hyperplastic in sternum and ribs. In tibiæ fatty marrow.

Microscopic Findings. *Brain.* Extreme dilatation and congestion of all vessels, particularly of the meningeal and pial. Diffuse thickening of the inner meninges. Chronic leptomeningitis.

Cord. Marked congestion of all vessels, particularly of the meningeal. Diffuse thickening of the meninges.

Heart. Hypertrophy. Brown atrophy. Fibroid patches. Healed syphilitic myocarditis. No active areas.

Aorta. Advanced atherosclerosis with patches of active syphilitic mesaortitis.

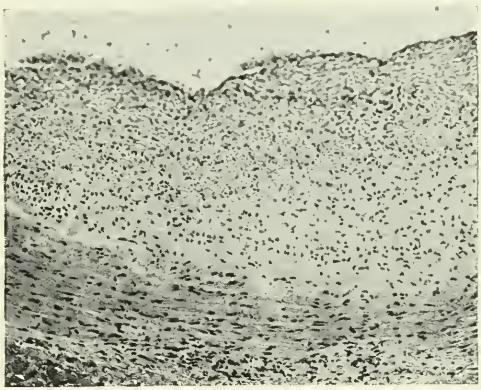

FIG. 1.—Main branch of pulmonary artery, showing extensive atherosclerosis and mesarteritis.

Lungs. Extreme chronic passive congestion with numerous pigmented phagocytes, "brown induration." Main branch of pulmonary artery shows extreme atherosclerosis of the intima and inner half of the media with active patches of syphilitic mesarteritis, and plasma-cell infiltrations around some of the vasa vasorum. The intrapulmonary branches of the pulmonary artery show extreme dilatation with marked atherosclerosis of the intima and inner one-half to one-third of the media. In the branches of the second and third degree a few small plasma-cell infiltrations around the vasa vasorum are found, but the majority of these branches show no active syphilitic lesions. The smaller branches of the pulmonary vessels are extremely dilated with thick hyaline walls showing no active process. (See Figs. 1 to 5.) The alveolar capillaries are greatly dilated, have thickened hyaline walls. In some areas the thickened alveolar walls present an appearance almost like that of a cavernous angioma. In other areas the alveolar walls are atrophic and hyaline, and the capillaries almost obliterated, the alveolar partitions extending into the dilated infundibula as stiff hyaline septa. (See Figs. 6 and 7.) In some portions of the lung, the circulation is completely shut off and the lung is fibroid and collapsed. Hemorrhages in all stages are found everywhere throughout the lung. There is marked edemas and great numbers of pigmented phagocytes

occur. Emphysematous areas are scattered through the indurated portions. The hyaline indurated portions of the lung are particularly the seat of anthracotic deposits. The bronchi and bronchioles are dilated and show catarrhal bronchitis. Small patches of early bronchopneumonia are

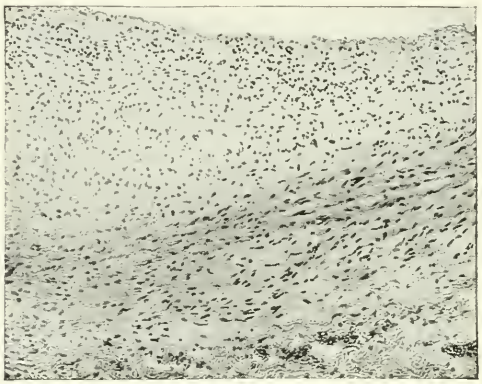

FIG. 2.—Medium-sized branch of pulmonary artery, at edge of sclerotic patch.

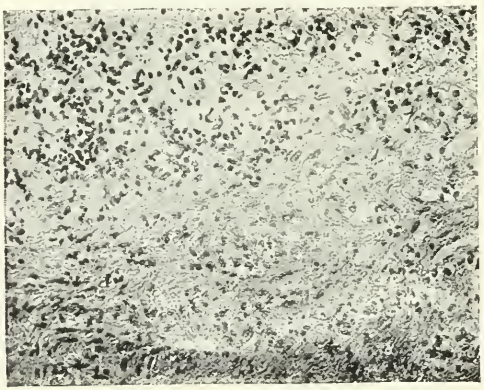

FIG. 3.—Media of main branch of pulmonary artery, showing area of plasma cell and lymphocyte infiltration of the media (syphilitic mesarteritis).

also found, particularly in the lower lobes. The pulmonary veins are extremely dilated and show hyaline, thickened walls without atheromatous changes.

Thyroid. Moderate amount of colloid. Extreme congestion of vessels.

Tongue. Numerous encapsulated trichinæ.

Spleen. Extreme dilatation of blood spaces and bloodvessels, many portions resembling an angioma simplex rather than spleen. The lymphoid tissue of the pulp is atrophic. The follicles are of fair size and the arterioles sclerotic. The larger arteries show hyaline thickening of their walls.

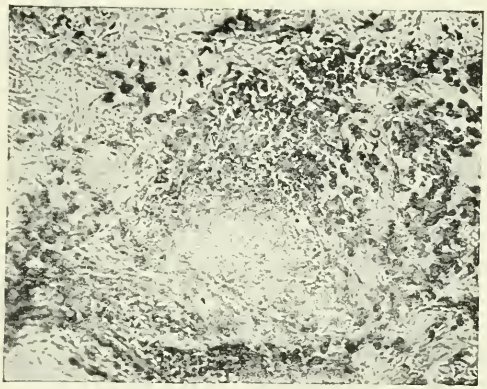

FIG. 4.—Plasma-cell infiltration about one of the vasa vasorum of the main pulmonary artery.

FIG. 5.—Dilated and sclerotic smaller pulmonary arterial branch.

Adrenals. Marked congestion, particularly in the reticular zone and medulla. Extensive medullary hemorrhage. The cortex shows extreme lipoidosis. Several small plasma-cell infiltrations are found in the reticular zone.

Kidneys. Extreme congestion, involving both arteries and veins. Marked hypertrophy of the glomeruli, many of the glomeruli being two or three times as large as normal, due to the increase in size of the capillary tufts. Majority of Bowman's capsules are thickened and there is a diffuse increase of con-

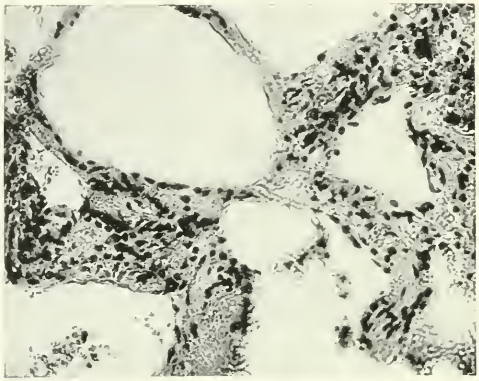

FIG. 6.—Air-containing portion of lung, with thick alveolar walls and some emphysematous alveoli.

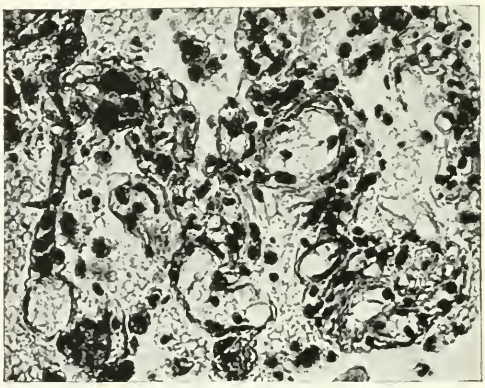

FIG. 7.—Atelectatic fibroid area of lung, showing the thickened sinusoidal capillaries.

nective tissue, with many scarred glomeruli, with definite areas of chronic parenchymatous nephritis. The vessels are all sclerotic. There is slight cloudy swelling of the convoluted tubules.

Stomach. Chronic catarrhal gastritis. Extreme congestion of both arteries and veins. In the stomach wall there are numerous areas of plasma-cell infiltration and localized induration, probably syphilitic.

Intestines. Extreme congestion of both arteries and veins. Slight catarrh.

Appendix. Extreme congestion of both arteries and veins. Thickening of submucosa.

Pancreas. Extreme congestion of both arteries and veins. Thickening of vessel walls. Fatty atrophy. Areas of marked intralobular interstitial pancreatitis, with some active plasma-cell infiltrations. Many islands of Langerhans are very large and show marked dilatation of the vessels.

Liver. Extreme nutmeg liver. Atrophy and necrosis of cells of central and intermediate zones. Dilatation of all vessels with atrophy and slight cloudy swelling of liver cells. Slight fatty degeneration, particularly of the central zones of the lobules. The capsule is thickened and just beneath the capsule the lobules are very atrophic and the periportal tissue shows proliferation, small-celled infiltration and new bile-duct formation, the picture being that of a localized, atrophic cirrhosis. These cirrhotic changes are found only beneath the capsule.

Prostate and Seminal Vesicles. Extreme dilatation of all vessels, with fibroid hyperplasia. In the seminal vesicles there are a number of retention cysts. The spermatic and prostatic plexuses show extreme angiectasis.

Testes. Extreme congestion and edema. Diminished spermatogenesis. Increase of stroma. Thickening of basement membrane. Early syphilitic orchitis fibrosa.

Lymph Nodes. All lymph nodes show extreme dilatation of the vessels, many of the retroperitoneal nodes resembling angioma. Atrophy of lymphoid tissue and increase of stroma.

Semilunar Ganglia. Extreme dilatation of vessels, increase of interstitial tissue and pigmentation of the ganglion cells.

Bone-marrow. That from the tibiæ consists of congested fatty marrow, with small islands of red-cell forming tissue. The sternal and rib marrow shows marked lymphoid hyperplasia.

Adipose Tissue. Reversion to fetal type. Congested and edematous.

Purpuric Spots. Telangiectasias.

Pathological Diagnosis. Plethora vera, Osler-Vaquez disease (erythremia; chronic cyanosis and splenic enlargement), secondary to syphilitic atherosclerosis of pulmonary arteries; emphysema and brown induration of lungs; cardiac hypertrophy and dilatation; chronic fibroid myocarditis; syphilitic aortitis; atrophy of pancreas with chronic interstitial pancreatitis; chronic syphilitic orchitis; chronic congestion of all organs; nutmeg liver; chronic splenic congestion; hypertrophy of kidneys, with chronic parenchymatous nephritis; chronic leptomeningitis; multiple telangiectasis of skin; hyperplasia of bone-marrow.

Epicrisis. This case presents the complete symptom and pathologic complex of the Osler-Vaquez disease in the form of a chronic

cyanosis, high degree of erythremia and splenic enlargement, with the secondary phenomena of dyspnea, visual disturbance, gastro-intestinal symptoms, general weakness, congestion, edema, etc. What is of great importance is the fact that the autopsy revealed a condition to which the Vaquez symptoms are most probably secondary. It can be very reasonably argued that, as the consequence of a widespread lesion of the pulmonary vessels, deficient oxygenation of the blood stream was produced. As a result of the need for oxygenation, secondary emphysema, hypertrophy of the right heart and increased activity of the bone-marrow developed as *compensatory conditions*. The *cyanosis* is an expression of the urgent need for oxygen; the *erythremia* is a compensation for this need; while the *splenic enlargement* is but a secondary result of the plethora and increased blood formation and destruction. The erythremia itself is brought about by an increased activity (hyperplasia) of the bone-marrow.

Further, the microscopic study of this case shows also the ultimate cause of the whole complex, in that the lesion of the pulmonary vessels presents the characteristics of a syphilitic mesarteritis. This diagnosis at present rests upon the histologic features alone. Levaditi studies of this material have been made, but no spirochetes have been found. Additional evidence of the presence of a syphilitic infection is to be found, however, in the characteristic myocarditis, mesaortitis, pancreatitis, adrenal infiltrations, chronic orchitis, and possibly also the chronic leptomeningitis. While the hospital records yield only negative statements as to the occurrence of a syphilitic infection in this patient, a letter from Dr. Frank Smithies, now of the Augustana Hospital, Chicago, tells me that this patient was one of the first to receive a Wassermann test in his laboratory, in Ann Arbor, and that the reaction was strongly positive (++++). From my own standpoint, however, the histological complex of heart, vessel, pancreas, adrenal and testicular changes can mean but one thing, a latent syphilitic infection.

The degree of arteriosclerosis and atheroma of the pulmonary artery and its branches shown by this case is, I believe, unique. I have been unable to find in the literature any description of pulmonary sclerosis in which the lesions appeared to be so severe and

extensive. In the case reported by me, "Syphilis of the Pulmonary Artery; Syphilitic Aneurysm of the Left Upper Division; Demonstration of Spirochete Pallida in Wall of Artery and Aneurysmal Sac,"[1] the sclerotic changes in the left upper branch were as marked, but in the other branches the degree of change was less. The microscopic appearances of the pulmonary vessel lesions were identical with those in this case and the demonstration of the spirochete was accomplished, both in the artery wall and in the aneurysm.

The literature of pulmonary arteriosclerosis is rapidly increasing, particularly in Spanish-American reports. It is noteworthy that in tropical countries clinical cases of pulmonary arteriosclerosis seem to be more common and syphilis is regarded as the common etiological factor. In my previous article I collected 4 cases of gumma of the pulmonary artery, 5 cases of gummatous arteritis, 15 cases of pulmonary arteriosclerosis regarded as syphilitic from the histological appearances or the association with other evidences of syphilis, and 51 cases of aneurysm of the pulmonary artery in which a syphilitic etiology was probable. (For literature, see article cited above.) In one of the reports, Rogers (1909) states that pulmonary arteriosclerosis is not a rare cause of fatal dropsy in Bengal, and expresses his belief that when it occurs between the ages of twenty and forty years syphilis is the etiological factor.

Sanders[2] reports 1 case from Dürck's laboratory and collects 7 cases from the literature (Klob, Crudeli, Wolfram, Romberg, Mönckeberg's 2 cases and Kitamura) of a primary sclerosis of the pulmonary arteries, with associated hypertrophy of the right heart. These were the only reports of such a complex that he was able to find. The cases are incomplete, both as regards clinical history and pathological study, in so far as the question of a syphilitic etiology is concerned. It was apparently excluded or not considered. Romberg's case was characterized clinically by *dyspnea*, *cyanosis*, and *enlargement of liver and spleen*. No mention of the blood findings. Mönckeberg's Case I, likewise, showed *cyanosis* with prominence of eyes and edema. His second case, a man, aged fifty-six years,

[1] Am. Jour. Syph., 1917, vol. i.
[2] Arch. Int. Med., 1909, iii, 257.

presented marked *cyanosis, edema, dyspnea* and *palpitation*, with *enlargement of liver.*

Although these cases are incomplete and the condition of the blood is not stated, it seems probable that some of them at least fall into a class showing the syndrome of *chronic cyanosis, dyspnea, erythremia* and *pulmonary sclerosis* recognized in Spanish-American literature as "Ayerza's disease" (cardiacos negros), from the fact that in a lecture given in his clinic, in 1901, Abel Ayerza, professor of clinical medicine, National University of Buenos Aires, was apparently the first to recognize the clinical entity of this syndrome. As far as I have been able to discover, the first published use of the term "Ayerza's disease" is in a doctoral thesis by C. A. Marty, "La Tension Arterial en la Tuberculosis Pulmonar," Buenos Aires, 1909, p. 45, in which he says there is a special group of cases, worthy of attention, of increased pulmonary arterial tension associated with hypertrophy of the right heart, pulmonary arteriosclerosis and chronic cyanosis, described eight years previously by Ayerza as "cardiacos negros." The designation is also used by Escudero in his *Conferencias Clinicas*, Buenos Aires, and by Garcia del Real, *Tratado de Patologia Medica*, Madrid, 1917, iv, 495–530.

Barlaro,[1] reports "A case of Ayerza's Disease," characterized by *extreme cyanosis, asthma, intense dyspnea, cardiac hypertrophy, erythremia* (red cells 6,600,000), *enlargement of liver*, spleen not palpable, *Wassermann* +++++, with *pulmonary arteriosclerosis.* He discusses the differential diagnosis of Vaquez's and Ayerza's diseases and concludes that many cases of Vaquez's disease are really cases of Ayerza's disease. He so regards the first case reported by Vaquez, the case of Parkes, Weber and Watson, Vaquez and Lanbrey, Saundby and Russel, Osler ("Erythremia without Splenic Enlargement") Herringham and others. Barlaro's point seems to be that cyanosis and bronchial pulmonary dyspnea have nothing to do with a primary polycythemia; if they exist in association the explanation of the condition is to be sought in conditions of the pulmonary artery (Ayerza's disease). While his case was undoubtedly one of syphilis, Barlaro is not sure that all cases of

[1] Revista de la Asociacion Argentina, 1917, xxvi, 121.

Ayerza's disease are syphilitic or secondary to a parenchymatous lesion. He draws analogy to Raynaud's disease and thinks "Raynaud's disease in the lungs" might account for some of the cases presenting the Ayerza syndrome.

The most complete description of the Ayerza syndrome is to be found in the monograph *Esclerosis Secundaria de la Arteria Pulmonar (Cardiacos Negros)* by F. C. Arrillaga, Buenos Aires. Eleven cases of pulmonary sclerosis, with extreme cyanosis, dyspnea and erythremia (in five cases in which a blood count was made) are described, beginning with the case seen by Ayerza in 1901. The author concludes that there can be no doubt as to the existence of a morbid entity called "Cardiacos Negros" and first described by Ayerza in 1901, characterized by *cyanosis, hyperglobulism, dyspnea, cough with expectoration of mucous or mucopurulent sputum, headache, angina hypercyanotica, hemoptysis, vertigo, insomnia,* etc. The patients present first a pulmonary evolution extending over a long period, then an evolution of the cardiacos negros state lasting, as a rule, two to five years. The patients may die sleeping, without edema, after presenting a galop rhythm of the right heart; or death may take place from early myocardial degeneration with marked anasarca, or from a complication, the most common of which is bronchopneumonia. The chief diagnostic points in distinguishing from other forms of cyanosis are the classical history of antecedent symptoms and the tempo of evolution of these, and the fact that the cyanosis is acquired and not the final episode of an asystolic condition, as in other forms, but is an initial symptom. The enormous hypertrophy and dilatation of the right heart is the most important objective sign in favor of a pulmonary rather than a peripheral obstruction. Radiography easily settles the diagnosis. The difference between acute dilatation of the heart is shown by the tempo of evolution and the immense dilatation of the veins in this condition, while the "cardiacos negros" have almost no veins. As to the etiology, the lesions in the pulmonary vessels may be secondary to chronic pulmonary disease, bronchitis, tuberculosis, pleural adhesions or any condition producing a final emphysema; or it may be the result of slow infections, as syphilis or malaria, or the result of intoxications.

SUMMARY. I am of the opinion that the clinical and pathological study of the case given in this paper separates it from the Vaquez group of erythremias into the class that Ayerza first pointed out as a distinct clinical and morbid syndrome. The long pulmonary evolution of the symptoms in the form of asthma and dyspnea, the later slow evolution of the cyanosis, erythremia and secondary symptoms, are characteristic of the Ayerza cases. The autopsy revealed a unique picture of extreme atherosclerosis of the pulmonary arteries, and the microscopic study shows the picture of a latent syphilis. The radiograms should have revealed the condition at first, had any one at that time heard of Ayerza's disease. The original radiograms have disappeared, but a pencil sketch which remains of the shadows, seen and interpreted as a mediastinal tumor, is almost a duplicate of the radiographic illustration (Fig. 9) in Arrillaga's monograph, in which the shadow of the dilated pulmonary artery is very well shown.

The erythremia in Ayerza's disease is beyond question a secondary compensatory process, an increased functional activity of the bone-marrow to meet the deficiency in oxygen supply due to the obstructed pulmonary circulation. It is most probable that this is the case in all forms of Vaquez's disease; certainly in all of those in which there is cyanosis and dyspnea. Neither one of these symptoms belongs to a primary erythremia; and when they are present it is certain that the erythremia is secondary. Likewise, the splenic enlargement is not an essential feature of the syndrome; it is also secondary, and its appearance in the disease may be early or late, according to varying conditions of congestion and increased splenic function.

The Osler-Vaquez complex of cyanosis, erythremia and splenic enlargement is a syndrome having a varied pathology and etiology, and is not a specific morbid entity. From Vaquez's disease there can be separated a group of cases showing the Vaquez syndrome associated with atherosclerosis of the pulmonary arteries and possessing distinctive clinical and diagnostic features. To this group of cases the designation "Ayerza's disease" or "Ayerza's syndrome" should be applied.

DISCUSSION

Dr. Libmann stated that one of the first cases of diffuse atherosclerosis of the pulmonary arteries was described by Neubauer in a case that had been mistaken clinically for a congenital defect of the heart. According to the literature, atherosclerosis of the pulmonary arteries was not infrequent in Bengal.

COMPENSATORY HYPERTROPHY OF THE THYROID GLAND

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(ABSTRACT)

1. The data concerning compensatory hypertrophy of the thyroid gland available at the present time are very contradictory. The conflicting character of the statements of different investigators is principally caused by the fact that the thyroid of dogs has hitherto been used in the large majority of investigations and the thyroid of the dog is liable to spontaneous hypertrophy. In our investigations the thyroid gland of the guinea-pig has been used. No case of spontaneous hypertrophy has so far been observed in this species.

2. In order to obtain definite hypertrophy of the thyroid in guinea-pigs it is necessary to extirpate both thyroid lobes and to leave only small remnants. The hyertrophy can be observed in many cases on the sixteenth or seventeenth day and in some cases even as early as between the eighth and fifteenth day. In some animals hypertrophy does not take place. Sickness of the animals is one of the causes of lack of hypertrophy.

3. Hypertrophy of the thyroid gland in the guinea-pig seems to have a definite cycle. Two months after the operation the gland is beginning to return to the accumulation of colloid in the acini, although the cells are still hypertrophic.

4. If we extirpate three-quarters of the thyroid the remaining one-fourth usually does not show marked hypertrophy, but shows the beginning of hypertrophy. In one case, however, a more marked hypertrophy was observed under these conditions.

After extirpation of one lobe the remaining lobe shows possibly

traces of a beginning change. These latter changes are, however, so slight that they may lie within the limits of normal variations in the thyroid gland.

5. If we compare these data with the conflicting statements of previous investigators it becomes very probable that the conditions leading to hypertrophy of the thyroid in different species, although they differ in the kind of nourishment they take, are essentially similar, even as to quantitative factors.

6. Hypertrophy increases the mitotic activity of the thyroid cells, but only in the early stages of hypertrophy. The mitotic activity shows a definite curve which differs from that of the hypertrophy itself.

7. The conditions of hypertrophy in autotransplanted glands are similar to those found in remnants, even in a quantitative way.

8. Contrary to the views expressed by several authors, the physiological deficiency in the thyroid gland does not influence its transplantability. Glands can be autotransplanted just as well in those cases in which a sufficient amount of thyroid gland has been left as in other cases in which a deficiency has previously been created. The deficiency merely determines the presence or absence of hypertrophy in the graft.

9. The substances which cause hypertrophy of the thyroid gland show no individuality-specificity, hypertrophy taking place even after homoiotransplantation of the thyroid gland in cases in which a deficiency exists. But the homoiotoxins interfere with the life of the hypertrophic as well as with that of the non-hypertrophic gland. Lymphocytes and connective tissue destroy the hypertrophic gland, lymphocytes being attracted by the homoiotoxins of the hypertrophic gland as readily as by those of the non-hypertrophic gland.

It appears that in addition homoiotoxins may, in certain cases, interfere directly with the production of hypertrophy.

10. In two pregnant guinea-pigs in which the thyroids were extirpated, the thyroids of the fetuses did not show hypertrophy and it was very slight in the thyroids of the mothers. In most cases early abortion takes place after extirpation of both lobes of the thyroid in guinea-pigs.

11. Potassium iodide or iodine as such, if given in frequent doses to animals in whom the greater part of the thyroid has been extirpated, does not prevent hypertrophy of the thyroid gland. The feeding of thyroid tablets, on the other hand, does prevent hypertrophy.

Experiments on the effect of thymus have been started, but are not yet sufficiently far advanced to permit a definite conclusion.

RESULTS OF ANIMAL EXPERIMENTS IN INFLUENZA AND INFLUENZAL PNEUMONIA

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The animal experiments which have been carried out heretofore with bacteria isolated quite constantly in influenza, both in 1889 and 1918, have consisted largely of virulency and toxicity tests in which only the usual methods of injection were used, and in which sufficient attention was not directed to the time and method of cultivation before injection. Statements have appeared concerning the high virulency of organisms of the streptococcus group[3 7] and the ability of influenza bacilli to produce highly toxic products in cultures[15] and a tendency to produce lesions in the lung,[1 8] but little has been accomplished in the way of reproducing the clinical and pathologic picture of epidemic influenza.

Intratracheal injection has been employed only occasionally in previous studies, despite the fact that by this manner of injection of highly virulent pneumococci Lamar and Meltzer have produced the typical picture of lobar pneumonia in the dog, Winternitz and Hirschfelder in the rabbit, and Cecil and Blake in the monkey. Wollstein and Meltzer have produced bronchopneumonia with bacteria isolated from bronchopneumonia in man.

The results of subcutaneous, intraperitoneal, and intravenous injections, in my hands, show that the bacteria, particularly green-producing streptococci, isolated quite constantly in epidemic influenza, possess high and peculiarly invasive powers. They have a marked tendency to produce leukopenia, to localize electively in the interstitial tissue and epithelial cells of the alveoli and smaller bronchi, and to produce hemorrhage and edema in the lungs, as

symptoms of anaphylaxis and emphysema of the lung usually develop. Significant as these facts are, an accurate analysis of the effects of the bacteria and the precise rôle they play in influenza was possible only by the use of methods which simulate more closely the natural conditions, through the application of the bacteria to the normal uninjured epithelium of the lower respiratory tract by the method of intratracheal injection. The guinea pig was considered the most suitable animal available for this study, since its resistance to streptococcal infection and its reaction to bacterial poisons and anaphylaxis have been found to be quite similar to those in man.

There has been much discussion, based chiefly on the results of cultures, with regard to the relative importance of the four main types of bacteria isolated in this disease: green-producing streptococci, including pneumococci, hemolytic streptococci, staphylococci, and influenza bacilli. By a combined study of intraperitoneal injection in mice and guinea pigs and intratracheal injection in guinea pigs of sputum and lung exudates directly, and of the primary mixed culture of these, a fair knowledge of the degree of the invasive power of these bacteria has been obtained. Invasion by the green-producing streptococcus in pure or almost pure form occurred in most instances even when the bacteria were not present in predominating numbers in the material injected. In some instances invasion by hemolytic streptococci occurred, but always only when they were present alone or in predominating numbers, and more rarely by staphylococci, but also only when they were present in predominating numbers in the material injected. Invasion by influenza bacilli following injection of sputum or lung exudate which in some instances was proved to contain influenza bacilli has not occurred in a single experiment. Similar results regarding the relative invasive power of these species have been obtained by injections of pure cultures of each, and again the independent invasive power of influenza bacilli was found to be slight.

The effects of intratracheal injection of mixtures of these organisms as they occurred in sputum and primary cultures and of pure cultures of recently isolated strains varied within wide limits. The animals may be classified in four groups as follows:

Group 1. Those animals which showed slight symptoms and then recovered.

Group 2. Those animals which showed mild early symptoms and later suffered severe attacks.

Group 3. Those animals which showed severe and progressive symptoms of marked lung involvement.

Group 4. Those animals which showed extreme and rapidly fatal effects.

Group 1. The symptoms of the animals in this group were relatively slight, consisting in the main of moderate illness, loss in weight, usually some fever, moderate leukopenia, and slight or moderately increased respirations for a number of days, followed by complete recovery. The animals were found to be immune to subsequent injections of heterologous strains. Those anesthetized for examination showed relatively slight or no lung involvement; cultures from the blood were sterile, and those from the lungs were either sterile or contained few of the organisms injected. These findings may be considered to parallel the clinical findings in patients with relatively mild influenza in whom little or no lung involvement can be demonstrated and in whom immunity is conferred as in the animals.

Group 2 In the animals in this group the initial effects of the injection were more pronounced and lasted longer than those in the animals of Group 1, and some of the animals, instead of recovering completely, developed severe symptoms of respiratory involvement and died in from one to two days with anaphylactic symptoms, voluminous lungs, and hemorrhagic bronchopneumonia, or, more rarely, from hemorrhagic pleuritis. In others the symptoms of respiratory embarrassment progressed more slowly; many developed rhinitis, and later died from purulent bronchitis and well-defined bronchopneumonia, often with small abscesses, and more rarely from abscess and gangrene, or from emphysema with or without bronchopneumonia. The cultures from those animals which died of relatively acute symptoms in the pneumonic attack usually showed green-producing streptococci, the pneumonic lung showing localized abscesses or abscess, usually staphylococci, or staphylococci and streptococci, and the empyemas usually hemolytic streptococci with or without staphylococci. The findings in this group may be regarded as representive of the findings in the group of patients with

the more severe influenzal attacks who later develop influenzal pneumonia or, more rarely, well-defined bronchopneumonia with slight hemorrhagic edema, but with purulent bronchitis and localized abscesses or a single large abscess, or of empyema with or without bronchopneumonia.

Group 3. In this group the initial symptoms were severe and usually progressed without intermission until death occurred in from two to three days from an increasing intense cyanosis and respiratory rate or from marked respiratory embarrassment from anaphylactoid symptoms during which, in many instances, hemorrhagic edematous fluid escaped from the nose while the animals made violent efforts to breathe. The lungs were huge; in a few cases interstitial emphysema had occurred and extensive consolidation consisting of coalescing areas of pneumonia of different ages and intervening areas of hemorrhagic edema. The blood was dark and remained liquid for a long time. The postmortem and microscopic findings in this group were in every way like those described as typical of acute influenzal pneumonia in man.

Group 4. In this group extreme dyspnea often occurred almost immediately after injection of highly virulent cultures and their filtrates. The symptoms were quite typical of acute anaphylaxis and many of the animals died while making violent efforts to breathe, as a bloody fluid ran from the nose and mouth. The lungs were huge, a dark purplish red, and hemorrhagic and edematous throughout. The symptoms and postmortem findings resembled very closely those noted in patients who died soon after being taken ill, usually in the initial attack of acute hemorrhagic edema of the lungs before sufficient time had elapsed for the development of extensive consolidation.

The distress from lack of oxygen, the intense cyanosis, and the extreme efforts at respiration of many animals in the latter two groups reminded one of the picture presented at the bedside of patients dying from a rapidly filling lung who copiously expectorated a serous, bloody, frothy fluid, and who frequently sat up or left their beds in making violent efforts to breathe as death occurred.

The experiments with the filtrates of cultures show that under the proper conditions green-producing streptococci may be sufficiently

small to pass through bacterial filters which prevent the passage of *Bacillus prodigiosus* and that small numbers of the streptococci, when applied to the normal mucous membrane of the lower respiratory tract, are sufficient to produce the characteristic symptoms and pathologic changes in the lungs of guinea-pigs. Moreover, the results of the experiments with filtrates of cultures, pneumonic lungs, and sputum, and those on the mechanism of the production of respiratory involvement, show that the strains from influenza which have high invasive powers also have the power to produce anaphylotoxin or allied substances in large amount, as measured by intratracheal injection. Many findings in influenza, such as the expanded, hyperresonant, relatively immobile thorax, cyanosis, the sharp leukopenia, the delayed coagulability of the blood, and the voluminous lung, appear to be expressions of an anaphylactoid intoxication.

The effects following injection of the control strains of green-producing streptococci, hemolytic streptococci, staphylococci, and type pneumococci in like dosage were very different. The immediate symptoms were less marked or absent, the mortality rate was much lower, leukopenia rarely occurred, leukocytosis was the rule, respirations while rapid in some instances were usually free and easy, prolonged anaphylactoid symptoms did not occur, and hemorrhages from nostrils were not observed. The lungs were smaller, the exudate more cellular, the areas of consolidation occurred earlier and were more definitely outlined, and there was either no edema or relatively slight hemorrhagic edema at all times. The contrast between the gross and microscopic picture of the lung following injection of highly virulent green-producing streptococci from influenza and of type pneumococci was particularly striking. In the former there was huge dilatation of the lung and alveoli, marked desquamation, and degeneration of alveolar epithelium, necrosis of alveolar capillaries associated with peripherally placed streptococci in large numbers, and hemorrhage and edema everywhere with relatively slight leukocytic infiltration dominating the picture. In the latter the striking findings were moderate distention of the lung and alveoli with slight degeneration of epithelium and little change in interalveolar capillaries, but with marked diffuse, sharply

demarkated, highly cellular exudate filling the alveoli, with the pneumococci diffusely distributed in the exudate, and with little edema.

The occurrence of marked lesions of lungs, including well-marked pneumonia, following injection of pure cultures of staphylococci, the presence of staphylococci in areas of softening in lungs injected with mixtures, and in large numbers in the sputum in some cases, but more particularly in the lung exudate after death, are in accord with the findings of Chickering and Park in *Staphylococcus aureus pneumonia*, and emphasize anew the importance of the staphylococcus as a cause of death and a factor in the production of lesions in the lung in epidemic influenza.

The theory that influenza and influenzal pneumonia are manifestations of the same infection, varying only in degree, is supported by these experiments. The bacteriology of the sputum and other exudates in influenza and in the early stages of influenzal pneumonia have been found to be identical. The infecting powers of the strains isolated in these two conditions, particularly of the green-producing streptococci, have been found to be very similar. The mortality in the guinea-pigs injected with strains from influenza is as high as in those injected with strains from patients with influenzal pneumonia who recovered. The mortality in the guinea-pigs was proportionately higher in those injected with material from patients who died than from those who recovered. The leukocyte curves in the fatal and non-fatal infections in the guinea pig ran parallel with the leukocyte curves in fatal and non-fatal infections in persons.

From a study of 266 severe cases of influenza and influenzal pneumonia treated in the hospital, in which accurate record of the exact onset of the attack was obtainable, it was found that 145 patients either had no preceding influenzal attack or developed outspoken signs of pneumonia within three days from the onset of symptoms; 108 became ill with pneumonia after an interval of from four to nine days, and 13 only had an interval ranging from ten to twenty-one days. The number of patients who developed outspoken signs of lung involvement in the initial attack and without a quiescent interval is therefore large. By means of the more

refined methods of examination, such as the *x*-ray, the incidence of lung findings in the primary influenzal attack has been greatly increased. Indeed, the manifestations of the disease and the bacteriologic findings in some instances have led good clinicians to regard the so-called complications as the disease itself[6] and bacteriologists to look on the "secondary invaders" as the cause of sharp outbreaks.[7]

Through a painstaking study by various methods of injection, but particularly on intratracheal injection, of the infecting powers of the bacteria at hand in influenza and influenzal pneumonia throughout several epidemic waves, it has been possible to reproduce in animals* the picture of influenza as it is seen in humans. The symptoms both of influenza and influenzal pneumonia have been closely simulated in these animals as far as is possible. The gross and microscopic changes described by Lord as they occurred in previous epidemics of influenza and by MacCallum, LeCount, Bell, and Lucke, Wight, and Kline, and others during the recent epidemic and which have come to be regarded as quite characteristic of influenzal infection have been reproduced in detail. The same varied picture which often supervenes in the later stages of influenzal pneumonia in man, such as leukocytosis as evidence of pleural involvement and purulent infection, becomes manifest, and the varied pathological picture in the lung of patients who died late have been noted in guinea-pigs injected intratracheally with these strains. The tendency to involvement of the female generative organs, with a high mortality during pregnancy and a high incidence of abortion, of lesions of the heart, abscess in the rectus muscle and interstitial emphysema have been noted in the experimental animal quite as these occur in humans.

* A complete report of these experiments will be published in a forthcoming number of the Journal of Infectious Diseases.

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A STUDY IN WAR NEPHRITIS: URINARY TRACT PURPURA; A PROBABLE CLINICAL ENTITY[1]

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AND

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In the summer of 1917 we began a clinical analysis of all the cases that were admitted to No. 1 British General Hospital at Etretat, with a diagnosis of nephritis or an allied condition. We hoped, by careful observation, to be able to satisfy ourselves that "War Nephritis" and "Peace Nephritis" were indistinguishable, or else to find one or more distinctive conditions that warranted more intensive study. One such condition we believe we have found.

Early in the course of our work we received a patient with profuse hematuria who complained of symptoms strongly suggesting vesical calculus or papilloma. Cystoscopic examination revealed neither stone nor neoplasm, but, instead, multiple submucous hemorrhages in the bladder wall, and blood pouring from both ureters. We have found altogether 25 cases with this same picture and 11 others that were similar in most respects. The clinical picture presented by these patients, if they be considered as a group, was entirely different from that of ordinary acute nephritis. Although cylindruria and reduction of the phenolsulphonephthalein excretion were consistently found, edema, dyspnea and uremic manifestations were noticeably lacking. The predominant symptoms, and the only constant ones, were profuse hematuria, and pyrexia of an irregular and vari-

[1] From No. 1 (Presbyterian, U. S. A.) General Hospital, U. S. Base Hospital No. 2, B. E. F., Etretat, France.

able type. We later established the existence of the disease also among American troops in France.

Careful histories revealed no suggestion of any predisposing etiological factors.

In most cases the onset was sudden, with a complete development of the disease within forty-eight hours. In some urinary symptoms were preceded for from twelve to forty-eight hours by general symptoms. The complete picture of the disease at onset showed marked prostration and general malaise, headache, pains in the legs and back, gross hematuria, frequency and urgency of urination, dysuria and pyrexia. The order of appearance of the symptoms varied, as did their relative severity.

Pains were of two types: those that seemed to be due to the effects of a general infection, and those that were referable to the urinary tract. The former presented themselves as severe headache and general pains with a tendency to localization in the back and limbs, sometimes associated with tenderness or hyperesthesia. They usually ended with the first bout of fever.

The urinary pains varied from dull aching in the lumbar region and the upper abdomen to the acute, lancinating pain of renal or vesicle colic, and were sometimes attended by marked tenderness over the kidneys or bladder. A very large proportion of the cases suffered from severe dysuria and frequency and urgency of urination, which usually ceased shortly after the gross hematuria, but occasionally persisted longer.

Herpes labialis occurred in 3 cases. With these exceptions the skin and mucous membranes were clear except for the usual pediculosis and scratch marks. No hemorrhages were found in the skin, visible mucous membranes or retina, in spite of repeated examinations.

Signs of respiratory disease were found in only 3 cases and, in these, bore no evident relation to the urinary condition. There were no signs of cardiac involvement and the blood-pressure was never elevated above normal limits.

In one instance there was an initial diarrhea, and, in a few others, occasional nausea and vomiting. No gross blood was found in either stools or vomitus. The spleen was found enlarged only once, and

then in the presence of an intercurrent infection of herpes. The liver was never found enlarged, nor was jaundice ever present.

Although there was often tenderness over one or both renal regions, the kidneys were never definitely felt.

The initial temperature was usually high and fell rather rapidly in most cases. Slight relapses of temperature to 99° or 100° (by mouth) occurred in all cases and were noted as late as the sixty-first day of the disease.

All the patients exhibited gross hematuria in the early stages of the condition. This lasted from three to fourteen days; but microscopic blood was observed in the urine as late as the sixty-third day of the disease. Only occasionally was any considerable number of leukocytes seen, and never frank pus. All but one patient showed granular and hyaline casts and, in most cases, red blood cell casts were also found. Sometimes the urine became negative for a period, with a later recurrence of albumin, casts and red blood cells. Albumin was seldom very marked and, in most cases, could be fully explained by the amount of blood present in the urine.

Only one patient was discharged from the hospital with consistently negative urinary findings and without symptoms. The termination of the period of observation varied from the eleventh day of the disease to the one hundred and eleventh.

In all but 4 cases there was a definite diminution in the excretion of phenolsulphonephthalein, the output varying from 13 to 48 per cent. in two hours. An improvement of function usually occurred with convalescence.

From the catheterized bladder urine of 10 cases staphylococci were obtained four times. Although the strictest precautions were observed, it seems safer to regard these as contaminations, especially as the organisms were seldom found in all the media used, and subsequent cultures from the same subjects proved negative, when taken.

Giemsa and Fontana stains failed to reveal spirochetes in the urinary sediment, and injection of urine from 3 cases into guinea-pigs was equally unsuccessful. Blood cultures were negative in 8 cases.

There is, apparently, no leukocytosis. Late in the disease a secondary anemia occurs.

Conditions did not permit a study of the chemistry of the blood or urine.

Cystoscopies were done from four to nineteen days after the onset of the illness. In all, essentially the same picture was found: multiple small hemorrhages into the bladder mucosa, unaccompanied by ulceration, neoplasm, calculus or signs of inflammation. The hemorrhages numbered from two to over fifty, were irregular in shape, and ranged in size from petechial spots to 1 cm. in diameter. They occurred chiefly on the posterior and posterior-lateral walls of the bladder, and frequently involved the trigone. They were often adjacent to or interrupted the course of the visible bloodvessels.

When gross hematuria existed at the time of cystoscopy blood was clearly seen to come from both ureteral orifices.

A second bladder examination was made in 6 of the 17 cases considered. In 1 or 2 cases new hemorrhages were found in the bladder late in the course of the disease.

Urethroscopy was done six times, and in 3 cases well-defined hemorrhagic spots were found in the posterior urethra.

By means of a small punch, operated through the cystoscope, we obtained specimens from the hemorrhagic spots in 7 cases. On section the mucosa was normal and unbroken. Where the bleeding had been recent, a profuse and patchy infiltration of well-preserved red blood cells appeared in the submucosa. There was no leukocytic infiltration and nothing suggesting an inflammatory lesion. The bloodvessels were usually somewhat engorged. In one specimen small nodular accumulations of degenerating connective-tissue cells and wandering cells were found in the vicinity of the small arterioles, and there was indication of the formation of a mural thrombus in one of these vessels.

Two specimens from patients with hemorrhages of longer standing presented degenerative changes in the connective-tissue cells of some of the medium sized vessels.

That the changes observed were not due to mechanical factors connected with the use of the punch we determined by comparison with specimens of normal bladder mucosa obtained from cases cystoscoped in other conditions. The lesions differed from the hemorrhagic spots in specimens obtained from a bladder which was

the seat of a cystitis; in fact, the latter showed a marked leukocytic infiltration. In 9 cases that approximated very closely the clinical picture above described, no hemorrhages were found in the bladder wall. Although these hemorrhages are the only really distinctive feature of the condition, it is more than conceivable that cases may occur in whom no lesions are found lower in the urinary tract than the kidneys and ureters, just as there are others in whom the lesions extend as far down as the urethra. Moreover, in these cases the cystoscopic examinations may have been made during intervals in which affected bladders were free from hemorrhages. (In the other cases positive urinary findings frequently continued after the bladder wall had become entirely clear.)

In one case with typical bladder hemorrhages there was evidence that the hemorrhagic condition was not confined to the urinary tract, but involved also the cerebrum. Another conformed to type only at the very beginning of his illness, when his symptoms were entirely confined to the urinary tract. Later he developed a general purpuric condition that was rapidly fatal. It may be that we are dealing with a hemorrhagic disease which usually reveals itself only in the urinary tract, but in severe cases also affects other organs. (With the above exception, the disease, as we saw it, was without mortality.)

The consistent presence of casts in the urine and the reduction of the phenolsulphonephthalein excretion indicate a nephritis; but a nephritis that differs in very essential respects from the ordinary types of acute nephritis seen in civil life or among the admissions of a General War Hospital. Although we cystoscoped thirty other patients who had typical nephritis with hematuria, none of them showed bladder hemorrhages. The absence of pus in the urine, the absence of leucocytic infiltration about the bladder lesions and the negative urine cultures argue against the common forms of urinary infection due to pyogenic organisms.

The temperature and associated symptoms give one the impression of a general toxemia, probably of infectious origin.

Of course, the evidence that we are dealing with a clinical entity is merely circumstantial; but the appearance in a considerable number of cases, of a distinctive pathologic and clinical syndrome,

hitherto unreported, is hardly conceivable as a fortuitous series of coincidences. (In an analysis of 200 cases of nephritis, the admissions to No. 1 General Hospital in the course of about ten months, it was found that the cases here reported made up about 14 per cent. of all the nephritis and 27 per cent. of the acute nephritis, thus assuming very noticeable proportions.) The bladder hemorrhages cannot at present be distinguished from any other purpuric lesions; but a purpura of such frequent occurrence, which is apparently limited, in at least a large proportion of cases, to the urinary tract, is sufficiently extraordinary to command attention. (Only 2 other cases of purpura were found during the twenty months at Etretat.)

Conclusions: 1. An analysis was made of renal medical cases admitted to a British General Hospital in France over a period of ten months.

2. An apparently new disease, characterized by hemorrhages throughout the urinary tract, was disclosed.

3. This condition made up about 28 per cent. of the acute nephritis admitted to the hospital. In all, 25 typical and 11 atypical cases were observed.

4. The presence of the disease among American troops in France was established.

5. Attempts to determine the etiology of the condition or to connect it with any other known disease were unsuccessful.

6. It seems quite possible that cases of this disease may occur also in civil life.

W Osler

THE INFLUENCE OF DR. OSLER ON AMERICAN MEDICINE[1]

By GEORGE M. KOBER, M.D.
WASHINGTON, D. C.

Dr. Osler has passed his seventieth goal post. Sincere personal appreciation of the master work of this chieftain in the art and science of medicine, gratitude for the kindly inspirations experienced through his influence and the sanguine hope that his fair example may stimulate the younger generation to emulate his noble achievements, have prompted the writer to lay the wreath of tribute at the feet of this most deserving of septuagenarians.

Dr. Osler's Early Life and Student Days. William Osler was born in Bond Head, Ontario, July 12, 1849, son of F. L. Osler, clergyman of the Church of England. His were not only rare physical and mental characteristics through parental inheritance, but, as told him by his old and true friend, Dr. Jacobi, at the farewell banquet tendered him on May 2, 1905, "It is no mean felicity to be born with the imprint of virtue."

Those familiar with the portrait of Osler as a school-boy at Trinity College, and those fortunate enough to have been personally associated with him in later years, have read in that face innate qualities which not only endeared him to his friends, but, in the estimate of his dear old mother, "Were more precious than all his honors."

Osler's earliest school life was passed in the school of his native village, following which he went to Port Hope for a term or two in Trinity College School of that place, and later still he entered

[1] The portrait of Dr. Osler is printed by courtesy of the American Journal of the Medical Sciences, January, 1920.

Trinity University at Toronto. Devoted to his books during hours of class, he enjoyed his play with the "playful child let loose from school." Robust of health, his mind matured with equal pace.

On quitting Trinity College, young Osler entered the office of Dr. Bovell, at Toronto, as assistant, and there he inaugurated his medical studies, later matriculating in the School of Medicine of McGill University, Montreal, graduating in 1872.

We learn from his classmate, Professor F. J. Shepherd, that while a conscientious worker, Osler never passed for "a grinder." He was not particularly known for his devotion to books, nor were his efforts entirely focussed toward success in examinations, but his main attention was directed toward the postmortem room and to all hospital work within reach. He was beloved because of his social qualities, kindliness of disposition and characteristic sense of humor. Dr. Shepherd remarks: "While he did not graduate very high in his class, there is a note in the convocation that a special prize was awarded for his graduation thesis, because of the originality it displayed and the research it evinced, and because of the collection of pathological specimens accompanying it which were presented to the museum. In the light of his after studies it is interesting to note that some of these specimens, still in the college museum, concerned the ulcers of typhoid fever." As a student, Osler was deeply interested in comparative pathology, and as a teacher in subsequent years, often illustrated a point in human disease by a reference to a parallel condition in the lower animals.

How carefully he prepared himself for the practice of medicine and the professor's chair is evinced in the fact that, following his graduation, he spent two years abroad in study in the laboratory of the physiologist, Burdon-Sanderson, and attending the clinics of Jenner and Wilson Fox, Ringer and Bastian in medicine and the dermatological clinics of Tilbury Fox. In 1873 he took the degree of licentiate of the Royal College of Physicians in London. Thereupon he went to Berlin, where he studied pathology under Virchow, physiological chemistry under Salkowsky, and clinical medicine under Frerichs and Traube. In the early part of 1874 he continued his studies in Vienna under Bamberger, Hebra and other noted clinicians.

Dr. Osler as a Teacher at McGill University. Upon his return to Montreal, in 1874, he was appointed, at the early age of twenty-five, professor of the institutes of medicine at the McGill University, which included the course of physiology and a series of twenty lectures on pathology. In 1875–76 instruction in histology and demonstrations in physiology were added to his work and in the following year a summer course in pathological histology. Dr. Osler served from 1874–1875 as physician to the Smallpox Hospital of Montreal, and it is chronicled that he sacrificed his salary for the purchase of microscopes for his department at the University. Osler, himself, has said that a man should come into internal medicine by one of three ways: Physiological chemistry, physiology or morbid anatomy. He made himself proficient in all three of these branches, especially in pathology.

In the winter of 1875–76 his autopsy work began at the Montreal General Hospital and continued for eight years, with 1000 autopsies to his credit. In 1878 he was appointed physician to this hospital, and there began his career as a brilliant clinical teacher. A man with such firm scientific foundations, a comprehensive knowledge of the subject presented by him, and his personal magnetism could not fail to command the respect and esteem of his students and professional colleagues. He not only awakened interest and enthusiasm in modern scientific medicine among his hearers, but also among the members of the medical societies. Even before the completion of his thirtieth year he figured as a leader, and his influence was felt not only in Canada and the States, but merited for him later the appointment of regius professor of Oxford University. Osler's recollections of his early teaching career are charmingly and modestly set forth in an address delivered at the opening of the session of that school, September 21, 1899, twenty-five years after the faculty, as he declared, "With some hardihood selected a young and untried man to deliver lectures in the institutes of medicine.

"My first appearance before the class filled me with tremulous uneasiness and an overwhelming sense of embarrassment. I shall not forget the nice consideration of my colleagues and the friendly greetings of the boys, which calmed my fluttering heart. One permanent impression abides—the awful task of the preparation

of about one hundred lectures. After the ten to twelve with which I started had been exhausted I was on the treadmill for the remainder of the session. False pride forbade the reading of the excellent lectures of my predecessor, Dr. Drake, which with his wonted goodness of heart he had offered. I reached January in an exhausted condition, but relief was at hand. One day the post brought a brand-new book on physiology by a well-known German professor, and it was remarkable with what rapidity my labors of the last half of the session were lightened. An extraordinary improvement in the lectures was noticed, the students benefited and I gained rapidly in the facility with which I could quote the translated German. Four years later I was appointed on the visiting staff of the Montreal General Hospital. What better fortune could a young man desire? I left the same day for London with my dear old friend, George Ross, and the happy days we spent together working at clinical medicine did much to wean me from my first love. From that date I paid more attention to pathology and practical medicine and added to my courses one in morbid anatomy, another in pathological histology and a summer class in clinical medicine. I had become a plurist of the most abandoned sort, and by the end of two years it was difficult to say what I did profess, and I felt like the man to whom Plato applies the words of the poet:

> " 'Full many a thing he knew,
> But knew them only badly.'

"Weakened in this way I could not resist when temptation came from pastures new in the fresh and narrower field of clinical medicine. After ten years of hard work I left Montreal a rich man—rich in the treasures of friendship and good fellowship, and those treasures of widened experience and a fuller knowledge of men and manners which contact with the bright minds in the profession necessarily entails. My heart, or a good bit of it at least, has stayed with these treasures."

Dr. Osler in the University of Pennsylvania. In the summer of 1884 Osler received a call from the University of Pennsylvania. When the invitation to present himself as a candidate for the position of professor of clinical medicine at Philadelphia

reached him at Leipzig, Dr. Osler told us he was inclined to believe it a joke. Nor was he disabused of this notion until two weeks later a cablegram reached him to meet Dr. Weir Mitchell in London. He added, with his characteristic humor: "Boston measures men by brains, it is said, New York by baw-bees and Philadelphia by breeding." It was Mitchell's task to test his breeding. He did so by having him eat cherry pie, and noting how he disposed of the stones. As Osler disposed of them discreetly the breeding question was settled.

In 1884 Osler was elected to the Fellowship of the Royal College of Physicians of London and in 1885 was also chosen from the newly elected fellows of the college to deliver the "Gulstonian Lectures," a singular honor which he most efficiently discharged, selecting for his subject "Malignant Endocarditis." His lectures were based on his studies and material available in Montreal. No wonder that a man so highly honored by the Royal College had been chosen the year before to become an associate of Leidy, Pepper, Stillé and other leading lights. Osler's advent in Philadelphia marked a turning-point in the methods of teaching medicine not only in Philadelphia but in the States.

In Philadelphia, as in Montreal, as well said by his friend, Dr. James C. Wilson, he inspired his students with a craving for knowledge based upon facts of the ward, of the miscroscope, of the laboratory, of the postmortem room and also stimulated their interest in medical literature. He demonstrated how medicine should be learned and taught.

He also insisted, with the younger generation, by precept and example, that it is not necessary for every physician to be a practitioner in the ordinary sense, but that long years of hospital and laboratory work constitute a better equipment for the teacher and consultant.

Dr. Osler at Johns Hopkins Medical School. In 1889, at the age of forty, Osler was invited to Baltimore to take charge of the medical clinic of the Johns Hopkins Hospital. From this time out dates clearly his greatest activity and usefulness in professional work.

Professor William H. Welch advises us that when Dr. Osler came to Baltimore the main intention of the faculty was that the hospital should form an integral part of the medical school and that opportunities should be afforded for higher clinical training. It accordingly seemed expedient that students should be made part of the hospital machinery, and to Osler is due the credit of working out the details of the scheme. This, indeed, represents his contribution to medical teaching in America.

As in Philadelphia so in Baltimore, Osler's impression on the local profession was profound. The following tribute, found in the *Maryland Medical Journal* for June, 1905, attests this: "He has taught them the value of work for the sake of work; he has shown them the beauty of labor; he has been to them an ever-present example of right living and right thinking; he has shown by word and example the duty the physician owes his patient, his brother in the medical fraternity and the community at large; he has broadened the scope of the physician's calling and he has shown him that the good man and the good citizen must both be present to make the good physician possible."

Dr. Osler's Influence on Higher Medical Education. Over forty published essays and addresses bearing on medical education and medical history are sufficient warrant of Osler's keen interest in this subject.

He was ever a staunch advocate of higher premedical education requirements, extension of the period of professional study and the substitution of laboratory instruction for didactic teaching. In his "Essay on the Need of Radical Reforms in the Methods of Teaching Senior Students," he advises teachers "to give to students an education of such a character that they can become sensible practitioners."

Dr. Osler was convinced that it is the duty of a medical school to see that the senior student "begins his studies with the patient, continues them with the patient, ends them with the patient, using books and lectures as tools, means to an end."

He persistently maintained that the ideal hospital is one con-

nected with a medical school, with the professors members of the attending staff. In this connection he writes: "The work of an institution in which there is no teaching is rarely first class. It is, I think, safe to say that in a hospital with students in the wards the patients are more carefully looked after, their diseases are more fully studied and fewer mistakes are made."

Osler's methods of teaching clinical medicine fitted in admirably with the general policy of the faculty that the students should be made a part of the machinery of the hospital. As a result the clinical unit was maintained in the fourth year as taught by him, but the work transferred from the out-patient department to the wards. In Osler's judgment "each man should be allowed to serve for at least half of the session in the medical wards and half in the surgical wards. He should be assigned four or five beds, and under the supervision of the house physician he does all the work in connection with his own patients. One or two of the clinical units are taken around the wards three or four times a week by one of the teachers for a couple of hours, the cases commented upon, the students asked questions and the group made familiar with the progress of the cases. In this way the student gets a familiarity with disease, a practical knowledge of clinical medicine and a practical knowledge of how to treat disease."

Though Dr. Osler disclaims any credit for his teaching method, it is nevertheless unquestionable that had it not been for his wonderful personality, enthusiastic and effective leadership, American medical education might still be fifty years in arrear of that of Europe. It required a man of his broad vision, sound judgment, a devotee to his profession and a statesman in medicine to make converts to the cause of his revolutionary ideals. Dr. Arnold Klebs has deeded us in Garrison's history an admirable pen portrait of the doctor as clinical professor at the Johns Hopkins Hospital:

"Never can one forget the scenes in the out-patient department, where he stood surrounded by his boys, helping them as a friend in their struggles with some difficult case. He would go to one, put his arm around his shoulder and then begin a friendly inquiry, interspersed with humorous remarks and allusions to the work done

by special students on a given subject. Urging, encouraging, inspiring, so we saw him always exact, dogmatic never, and when the humorous, friendly fire kindled in his eyes we could not help but love him, and with him the task we had chosen for our life work."

We feel that we would be omitting an important page in the story of Osler's activities were we to pass over in silence those homely Saturday evening gatherings, held at the table round in his magnificent library, where he offered what Garrison characterizes as "the best models of charming essays on medical history," and estimated by Sudhoff "to contain more of the historical spirit than many learned works of the professional historian. The reason is that Osler loves his old authors as he does his profession."

These gatherings also enabled him to familiarize himself with the individuality of each student and in his charming way to offer timely and valuable suggestions as to how to solve certain intellectual and moral problems. Johns Hopkins Medical School has become known as the mother of medical teachers, and since 213 of the 453 graduates who were also his pupils prior to 1906, are or have been connected with our medical schools, it is easy to infer the extent of his beneficent influence.

Dr. Osler realizing, as every master mind necessarily must, the value of example, ever inculcated on his student body esteem for the general practitioner and old-style country doctor. Most of his pupils will cherish gratefully the words addressed to them during class hours: "Many of you have been influenced in your choice of a profession by the example and friendship for the old family doctor or of some country practitioner in whom you have recognized the highest type of mankind and whose unique position in the community has filled you with laudable ambition. You will do well to make such a man your example, and I would urge you to start with no higher ambition than to join the noble band of general practitioners. They form the very sinews of the profession—generous-hearted men, with well-balanced, cool heads, not scientific always, but learned in the wisdom of the sick room if not in the laboratories."

Osler was deeply interested in the progress of American medicine

and proud of its achievements, as shown in his address delivered at the opening of the Museum of the Medical Graduates' College and Polyclinic in London on July 4, 1900, in which he pointed out the silent revolution which had taken place in medical education, and especially in the cultivation of the scientific branches, hospital equipment and clinical facilities:

"The most hopeful feature is a restless discontent which, let us hope, may not be allayed until the revolution is complete in all respects. Meantime, to students who wish to have the best that the world offers, let me suggest that the lines of intellectual progress are veering strongly to the West, and I predict that in the twentieth century the young English physicians will find their keenest inspiration in the land of the setting sun."

It is quite natural that a man with such high hopes and aspirations would strongly resent any interference with the legitimate and humane methods employed for the advancement of scientific medicine.

I shall never forget the expression of scorn in his eyes and the words with which he rebuked the enemies of scientific progress, who had been heard before the United States Senate Committee on a bill for the further prevention of cruelty to animals: "The blood just surged in my veins, Sir, when I heard two men address you today, say things which they should have been ashamed to say of the medical profession, of men who daily give their lives for their fellows. . . . With reference to men who train with these enemies of the profession, I say this, that I scorn them from my heart." (See Hearing on Vivisection, February 21, 1900, Government Printing Office, Washington.) The bill failed in the committee and no serious attempt has been made to enact what Osler characterized as "a piece of unnecessary legislation."[1]

Dr. Osler's Influence on the Profession at Large. The many invitations extended and accepted by Dr. Osler to address

[1] Since the above was written a bill known as S. 1258, to prohibit experiments upon living dogs in the District of Columbia, was introduced and hearings were held before the Subcommittee of the Committee on the Judiciary, U. S. Senate, November 1, 1919, and it is hoped that the bill will not be enacted.

medical societies attest the savory, widespread influence his career wielded over the medical community at home and abroad. His text-book, *Principles and Practice of Medicine*, graces the bookshelves of well-nigh every English-speaking physician the world over.

The medical societies, the efficient vehicle, as he took it, for the dissemination of scholarship, ever received his heartiest encouragement. Accordingly, we find him either enrolled as an active member of these societies or fostering their foundation, because, as he said, to the members and friends on the occasion of the centennial celebration of the New Haven Medical Association, January 6, 1903: "The society is a school in which the scholars teach each other, and there is no better way than by the demonstration of the more unusual cases that happen to fall in your way." Through these societies he awakened interest in postmortem work, the presentation of pathological specimens and in library equipment. Through them, also, he emphasized what a well-equipped and properly manned hospital in every town of 50,000 inhabitants could effect toward the advancement of clinical medicine. Through them he felt that America would accomplish more for clinical medicine in five years than Germany could in ten.

Osler was one of the most active founders of the Association of American Physicians, organized at a meeting held in the office of Dr. Francis Delafield, New York City, October 10, 1885. Others present at this time were Drs. William H. Draper, William Pepper, James Tyson, George L. Peabody and Robert T. Edes.

The first scientific meeting of the Association was convened in Washington, June 17, 1886, and from that meeting until his departure for Oxford he was recorded absent from the meetings but twice. Even after his departure he attended several meetings, and was elected an honorary member in 1912. In 1894 he was elected president of the Association, and in his address delivered May 30, 1895, he spoke in part as follows:

"At the opening of our tenth meeting the question is timely—How far has the Association fulfilled the object it had in view? Have our aspirations and hopes of 1885 been realized? We sought, as stated in Article I of our Constitution, the advancement of

scientific and practical medicine. With this primary object we sought also, as Dr. Delafield said in his opening remarks, an association in which there will be no medical politics and no medical ethics; an association in which no one will care who are the officers and who are not; in which we will not ask from which part of the country a man comes, but whether he had done good work, and will do more, whether he has anything to say worth saying and can say it."

Osler believed that the nine volumes of the *Transactions* offered a full and satisfactory answer to the first question and referred to them as "the repository of very much that is best in American medical literature." He emphasized the widespread and effective interest which the papers of Dr. Fitz on "Appendicitis" and of Dr. F. M. Draper on "Pancreatic Hemorrhage" had produced, and succinctly reviewed some of the topics presented for discussion, such as typhoid fever, the parasites of malaria, tuberculosis, diseases of the gastric intestinal tract, diseases of the heart, blood, blood-vessels, kidneys, etc. He boldly stated that several papers had been presented which indicated that the readers had failed to grasp the scope of the Association. He declared that the Association had already shown a powerful influence on the study of pathological and clinical medicine in this country, that there was at present an actual scarcity of trained pathologists and bacteriologists and a distinct need of well-trained special clinical physicians, and of such physicians and of pathologists and bacteriologists should the Association in greater part be composed.

He referred to the limited membership, and with characteristic frankness declared: "We should all understand that this is a working society, and when any one of us ceases to attend regularly, or when our interest grows lukewarm, we will promote best the common welfare by quickly retiring."[1]

Osler was a member of the Council of the Association for a number of years and exercised a strict but just censorship over the

[1] The membership of the Association in 1886 was limited to 100, which was increased in 1897 to 125, in 1904 to 135 active and 25 associate members and further increased to 1912 to 160 active and 25 associate members. Active members after ten years' service may be transferred to the list of emeritus members. Honorary membership is limited to 25.

admission of members; he was doubtless the most active and fruitful worker in that body, as shown by ten original contributions and his discussion of sixty-four papers presented by other members. He was as popular among his colleagues in the Association as a teacher as with his classes in the medical school. The young and the old were attracted, inspired and improved, and men like Jacobi and others much older than he have told him that they were glad to sit at his feet and listen to him. Since the majority of these men were occupying professorial chairs the sphere of his beneficent influence has been greatly evidenced. He was also an enthusiastic founder of the National Association for the Study and Prevention of Tuberculosis in 1904, and has been the Honorary Vice-President ever since 1905.

When Osler, well-nigh fifty years ago, stood upon the threshold of his professional life, he stood there convinced of the dignity and responsibilities of his lofty avocation. He stood there convinced that if his name were to be dug deep in the marble walls of the hall of fame, it had to be dug therein with the chisels of study, honesty and truth. He has now lived a lifetime of life and lived it well. He has lived a lifetime of study as evinced by over seven hundred and thirty contributions to medical literature. He has lived a lifetime of service to his fellowman, to which bear witness his contributions to preventive medicine, his active participation in the eradication of preventable disease, his kindly ministrations to the sick poor. He has lived a lifetime which has been an honor to his profession and a glory to his professional brethren. A lifetime which has been rewarded with every honor and trust at home and abroad which the medical community could possibly bestow upon him. He has lived a lifetime of service, and during this lifetime he has tempered tenderness with firmness, condescension with authority. His only protest against cares was silence. Dignity met his responsibilities; equanimity his successes and griefs, sufferings and disappointments. And as our congratulations go out to him there follows the sincere hope that his days of activity and bliss may still be many to complement this lifetime that shall know no death.

Unfortunately the universal hope of Sir William Osler's friends that he might live long to enjoy the evening of his life has not been realized. It is, however, a comforting reflection that his life, so full of honors, was spared until after he attained the scriptural age of three score and ten. In the last year of his life he had the satisfaction of being elected to the presidency of the British Classical Association, "a singular and much appreciated honor for a medical man." An honor more highly cherished by him was the international celebration of his seventieth birthday, when on July 12 he received the felicitations and congratulations of the medical world and the Anniversary Volumes prepared by his students and colleagues.

In response to the presentation address, Dr. Osler said:

"To have had the benediction of friendship follow one like a shadow, to have always had the sense of comradeship in work, without the petty pinpricks of jealousies and controversies, to be able to rehearse in the sessions of sweet, silent thought the experiences of long years without a single bitter memory, fill the heart with gratitude. That three transplantations have been borne successfully is a witness to the brotherly care with which you have tended me. Loving our profession, and believing ardently in its future, I have been content to live in it and for it. A moving ambition to become a good teacher and a sound clinician was fostered by opportunities of an exceptional character, and any success I may have attained must be attributed in large part to the unceasing kindness of colleagues and to a long series of devoted pupils whose success in life is my special pride."

The writer cannot help but feel that the days of our beloved chief, like those of many other men and mothers, with courageous but sympathetic hearts, have been shortened by the cruel world war. He lost his only son and also a nephew on the western battle fields, and his silent but intense grief, combined with overwork, did much to undermine his constitution.

The first information of his impaired health reached me in a card dated November 19, in which he wrote: "I have been laid up for some weeks with bronchitis, but am better now." Pneumonia developed and later pleurisy, with effusion, necessitating a thoracentesis. On Christmas Day he sent a cheerful, hopeful telegram to

his friends at the Johns Hopkins Hospital, that he was making a good fight, but on December 29 came the end, at his home in Norham Gardens, which was felt as a shock throughout the English-speaking world. He has gone to his long home. Minerva Medica has ushered him through the portals beyond and proudly but reverently presented him to the Supreme Healer of the Universe as a type of the true physician, whose spirit will abide with us now and always!

FUNCTIONAL DIAGNOSIS OF POLYGLANDULAR DISEASE IN ACROMEGALY AND OTHER DISTURBANCES OF THE HYPOPHYSIS

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The unusual opportunity afforded by the admission of 5 cases of hypophyseal disease to our medical clinic in the course of a few weeks was the stimulus for the work. Whereas in the previous 6000 medical admissions there were 11 cases (0.18 per cent.), we were suddenly confronted with these 5 cases. One case studied in 1914 has been added to the 5 recent cases.

As neither time nor space will permit a detailed history of these 6 cases, we will content ourselves with a short summary of each case:

Case I.—J. J.; aged thirty-one years; male; farmer; not referred. Admitted December 23, 1914. Clinical No. 1814.

Summary Acromegaly; round-cell sarcoma of pituitary gland. Symptoms first of hyperpituitarism, followed later by hypopituitarism; characteristic changes in acra; somnolence; polyphagia; optic atrophy and divergent strabismus; sugar tolerance increased; sella turcica enormously enlarged; trans-sphenoidal operation attempted December 28, 1914, but interrupted because of patient's condition; death three months later, with symptoms of right-sided hemiplegia. Autopsy revealed an enormous pituitary tumor, with marked cerebral compression, atrophy of islands of Langherhans; atrophy of testes; slight cystic degeneration of thyroid gland.

The adrenalin conjunctival test was strongly positive for adrenal insufficiency, while both subcutaneous tests spoke for normal function. The pituitrin conjunctival and both subcutaneous tests suggested a hypopituitarism.

Case II.—Mrs. A. W.; aged fifty-two years; female; referred by Dr. Cretzmeyer, Algona, Iowa. Admitted January 10, 1919. Clinical No. 5808.

Summary. Acromegaly; hyperpituitarism; amenorrhea at thirty-nine years; severe frontal headaches since forty-eight, followed by failure of vision, enlargment of head, hands and feet, profuse night-sweats; typical facies; acra characteristic; hypertrophy of genitalia; fundi negative; sella turcica enlarged; slight glycosuria, with much decrease in sugar tolerance; normal renal function. Adrenalin conjunctival and subcutaneous tests indicate hypofunction of adrenals; pituitrin tests doubtful; posterior lobe caused subjective improvement.

Case III.—Mrs. O. H.; aged forty-seven years; not referred; Clinton, Iowa. Admitted March 8, 1919. Clinical No. 6009.

Summary. Acromegaly; hyperpituitarism. Symptoms for eight years; typical facies; slight goitre; acra much enlarged; divergent strabismus; greatly enlarged sella turcica; glycosuria; hyperglycemia; adrenalin conjunctival test spoke for a normal and the subcutaneous tests for a hypofunction of adrenals. The pituitrin conjunctival test was markedly positive, while of the subcutaneous tests the blood-pressure one was normal and the blood picture within possible normal limits.

Case IV.—James W. R.; aged twenty-nine years. Lineotype operator; referred by Dr. Fred Bailey, Cedar Rapids, Iowa. Admitted February 27, 1919. Clinical No. 5974.

Summary. Sarcoma of the occipitoparietal lobe; no localizing symptoms; diagnosis of hyperpituitarism from tumor of hypophysis made because of occipital and temporal headache, double papill-edema, distorted sella turcica and decreased sugar tolerance; transphenoidal decompression, followed in two weeks by death; autopsy revealed flattening of hypophysis from greatly increased intracranial pressure, which had thinned out even the sella turcica. Microscopically, hyperemia of the entire hypophysis, with hemorrhage by disapedesis into the pars nervosa. Adrenalin conjunctival test and one of the subcutaneous tests spoke for hypofunction of the adrenals. All three pituitrin tests were normal.

Case V.—Miss L. K., aged sixteen years; not referred. Admitted March 15, 1919. Clinical No. 6036.

Summary. Dystrophia adiposogenitalis; Froehlich syndrome; malaria and typhoid fevers in childhood; periodic diplopia, with headache, nausea and vomiting; amenorrhea at fourteenth year, followed by enlargment of breasts and rapid gain in weight of forty-two pounds; nycturia; facies and figure of hypopituitarism; convergent strabismus; transient glycosuria, marked decrease of sugar tolerance; sella turcica small; adrenalin conjunctival and subcutaneous tests spoke for normal adrenal function. The pituitrin conjunctival and subcutaneous tests were also within normal limits.

Case VI.—Mrs. M. L.; aged thirty-four years; referred by Dr. W. W. Daut, Muscatine, Iowa. Admitted May 5, 1919. Clinical No. 6225.

Summary. Dystrophia adiposogenitalis; Froehlich's syndrome; obesity; glycosuria; marked family history of obesity on maternal side and in sisters; amenorrhea, obesity, headaches, nycturia and glycosuria; signs of tertiary lues and old pelvic cellulitis; Wassermann negative; normal facies; normal hair except for hirsuties over face; slender extremities; sella turcica not enlarged; adrenalin conjunctival and subcutaneous blood picture tests spoke for normal function of the adrenals. The diminution of 14 mm. in systolic pressure cannot be explained. The conjunctival and subcutaneous pituitrin tests were normal.

A paper by Karl Csépai[1], which appeared in 1914, described a comparatively new method of investigation of the diseases of the endocrine glands and has been applied to our six cases, which form the material of this paper.

It seems hardly necessary to state that the determination of the sugar tolerance is as yet the most accurate and only scientific method for an estimation of the activity of the internal secretion of the hypophysis, thyroid gland and pancreas. It is not so long since that we first appreciated the frequency in hyperthyroidism of an alimentary glycosuria or even of a frank glycosuria, whereas in hypothyroidism a normal or increased sugar tolerance was observed. An excellent paper by H. R. Geyelin[2], in 1915, states that alimentary hyperglycemia and alimentary glycosuria are not uncommon in even the very mild cases of hyperthyroidism, and that in the moderate or severe cases a fasting or postprandial hyperglycemia was present in 90 per cent. of his series.

TABLE I

Diagnosis.	3 gtts. conjunctivally.		0.5 c.c. subcutaneously.		Carbohydrate tolerance.
	Adrenalin, minutes.	Pituitrin, minutes.	Adrenalin, mm. syst.	Pituitrin, mm. syst.	
Csépai's normal	+10–20	+ 0–10	+30–60		
Author's 15 controls	+10–30	+ 0–25	+ 3–42	−5–38	
Csépai's acromegaly, case 1	+15−	+25+	+60−	.....	Diminished.
Csépai's acromegaly, case 2	+10−	+15+	+70+	.....	Diminished.
Csépai's acromegaly, case 3	+35+	+ 8−	0−	.....	Normal or increased.
Csépai's dystro. adip. Gen. case 2	+35+	0−	0−	.....	Increased.
Author's acromegaly, case 1	+45+	+15+	+10−	0−	Increased to 300.
Author's acromegaly, case 2	+25+	+15+	+13−	− 8−	Diminished.
Author's acromegaly, case 3	+15−	+45+	+ 2−	−12−	Diminished with glycosuria.
Author's hyperpituitarism	+35+	0−	+14−	−10−	Diminished.
Author's dystro. adip. gen., case 1	+15−	0−	+28−	−13−	Diminished.
Author's dystro. adip. gen., case 2	+ 5−	+ 5−	−14+	−10−	Diminished with glycosuria.

Our knowledge of the relationship of the internal secretion of the pancreas to glycosuria and hyperglycemia dates back to the work of von Mering and Minkowski (1890) and E. L. Opie (1903) and has since then received absolute confirmation.

The rule of the hypophysis in carbohydrate metabolism was much more recently appreciated, although it had long been known that glycosuria was a frequent associated phenomenon of acromegaly. Thanks to von Noorden (1910) and Cushing (1912) the importance of the determination of the sugar tolerance for the diagnosis of a suspected disturbance of the hypophysis is now universally accepted. Further, as the result of the correlation of much experiemtnal work and many clinical observations, it seems definitely established that the pars intermedia is directly concerned in carbohydrate metabolism and the hypertrophy of it causes polyuria, diminished carbohydrate tolerance or even a frank glycosuria, while hypoplasia or degeneration of the pars intermedia will result in a high degree of sugar tolerance.

In the early stages of acromegaly, therefore, it is common to find a decreased sugar tolerance as did we in two cases of acromegaly, one of secondary hyperpituitarism and in the two cases of dystrophia adiposogenitalis. (See Table I.) On the other hand in the latter stages of the hyophyseal disease when the pars intermedia has been destroyed by pressure or by invasion, as occurred in our case of acromegaly from sarcoma of the pituitary gland, increased sugar tolerance is to be expected.

The method of sugar tolerance determination is too well known to require a detailed description. We accepted as the usual minimum normal limit 100 grams of glucose, which was administered to the fasting patient after an immediately preliminary examination of the urine and blood sugar; at hourly intervals blood and urine examinations were made for a period of four hours. Glycosuria and hyperglycemia, of course, indicate a decreased sugar tolerance; some even regard a slow return of the blood sugar content to its previous normal as also pathognomonic. If neither glycosuria nor hyperglycemia occurs one administers on successive days 200, 300 or even 400 grams of glucose. There is still some doubt as to the exact upper normal limit of the sugar tolerance, though it was

formerly considered to be 250 grams. It might therefore be safer to say that in our first case of acromegaly the sugar tolerance was normal or increased.

It is well to bear in mind that in spite of the unusually protected site that the hypophysis enjoys it is nevertheless susceptible to a disturbance of its function by greatly increased intracranial pressure from any cause, as internal hydrocephalus, tumor of the brain or of the adjacent tissues. Case V of our series was first considered to be a tumor of the silent area of the brain, but eventually the discovery of a flattened sella turcica and a decreased sugar tolerance seemed to justify a localization of the tumor in the region of the pituitary gland; accordingly a transphenoidal decompression was undertaken. Though the postmortem three week later revealed a large sarcoma of the white matter of the occipitoparietal lobe, it was also found that the tremendous increase of intracranial pressure had not only thinned out the vertex of the skull to almost egg-shell transparency but had also completely flattened out the sella turcica and its contents and so produced a general hyperemia of the hypophysis with hemorrhage into the pars nervosa. We were therefore justified in a diagnosis of secondary hyperpituitarism.

The two methods suggested by Csépai were the conjunctiva instillation of adrenalin or pituitrin and the subcutaneous injection of both.

The Conjunctival Adrenalin Test. In several hundred controls Csépai found that normally three drops of a 1 to 1000 solution of adrenalin will cause in a few minutes a slight or moderate blanching of the conjunctival sac, which will persist for ten or twenty minutes. The procedure is very simple and is, as a rule, easily and rapidly performed. The patient should be asked to keep both eyes closed for five minutes before the test. Further, only one conjunctiva is instilled, the other one being used for comparison.

My assistants used as normal controls fifteen medical patients who showed no evidence of polyglandular disease. The controls were suffering from chronic bronchitis (two cases), gastric neurosis (three cases), lupus vulgaris, amebic dysentery, cardiorenal disease, secondary syphilis, tabes dorsalis, lethargic encephalitis, osteochondroma, peptic ulcer, cholecystitis and diabetes mellitus (one case each). We found that the duration of the blanching was not

so constant as Csépai states, and varied from ten to thirty minutes. (See Table I.) In fact, this upper limit was observed in four of the fifteen cases. Further, in one normal case, a girl with chronic bronchitis, there was no definite blanching on one occasion and on another test blanching occurred and lasted for twenty minutes. These discrepancies may be due either to errors in technic or to variations in the strength of the adrenalin solution. It is perhaps opportune here to state that all these tests were carried out by four well-trained interns (Dr. R. D. Taylor, Dr. A. W. Bennett, Dr. R. H. Gray and Dr. E. J. Voigt), who did not know what to expect, and only two of whom studied more than one polyglandular case and two normal controls, so that the personal equation was fairly well excluded. Further, only fresh adrenalin and pituitrin were used.

Exaggeration of the reaction indicates, according to Csépai, a diminished function of the adrenal glands. He noted a blanching of the conjunctiva of thirty-five minutes' duration in one case of acromegaly and in one case of adiposogenitalis, and of thirty minutes' duration in a case of Addison's disease and in one case of myxedema. In our series of six cases it was normal three times, slightly prolonged (twenty-five minutes) once, and decidedly prolonged (thirty-five to forty-five minutes) in two cases. (See Table I.)

Csépai also noted that in the cases in which the adrenalin reaction was positive (*i. e.*, the blanching prolonged) the carbohydrate tolerance was increased or normal. This relation did not hold for our series, for in only one of the positive cases was the carbohydrate tolerance increased while in the other two there was a distinctly decreased sugar tolerance.

The Subcutaneous Adrenalin Test. It has long been known that the subcutaneous injection of 5 mg. of adrenalin is followed by a prompt increase in both diastolic and systolic blood-pressure as well as increase in the pulse-rate. Csépai found an increase of 30 to 60 mm. in the systolic pressure in normal cases. Such a pronounced increase we could not find in our twelve normal controls. Our increase ranged from a maximum of 42 to a minimum of 3 mm., or an average increase for the series of only 17 mm. in the systolic pressure. As a rule the diastolic pressures followed closely the systolic. (See Table I.)

TABLE II.—ADRENALIN SUBCUTANEOUSLY.

Diagnosis.	Blood picture before.						Blood picture two hours after.					
	Total W. B. C. per cu. mm.	P. N., per cent.	Ly. per cent.	Tr.andLM. per cent.	Eosin, per cent.	Mz. per cent.	Total W. B. C. per cu. mm.	P. N. per cent.	Ly. per cent.	Tr.andLM. per cent.	Eosin per cent.	Mz. per cent.
Average 8 positive controls	+1,880	76	27.0	1.5	0.75	0	.....	78	22.0	1.0	0.3	0
Average 4 negative controls	−1,200	70	25.0	1.7	0.25	0	.....	71	27.0	2.5	0.2	0
Csépai's acromegaly, case 1	5,100	38	48.0	4.0	8.0	2	4,800	69	24.0	4.0	3.0	0
Csépai's acromegaly, case 2	6,000	62	33.0	3.0	2.0	0	7,000	67	27.0	1.0	5.0	0
Csépai's acromegaly, case 3	4,700	54	35.0	5.0	5.0	1						
Csépai's dystro. adip. gen., case 1	5,100	54	39.0	5.0	2.0	0						
Csépai's dystro. adip. gen., case 2	4,200	31	48.5	12.0	5.5	3	6,800	63	26.6	8.8	1.2	4
Author's acromegaly, case 1	6,000	52	35.0	9.5	3.5	0	9,600	61	33.0	6.0	0.0	0
Author's acromegaly, case 2	5,080	62	32.0	4.0	1.0	0	4,200	67	30.0	3.0	0.0	0
Author's acromegaly, case 3	7,900	77	18.0	4.0	0.0	0	6,200	76	19.0	4.0	1.0	0
Author's hyperpituitarism	8,600	69	28.0	2.0	1.0	0	9,800	76	22.0	2.0	0.0	0
Author's dystro. adip. gen., case 1	4,900	70	26.0	1.0	3.0	0	5,600	74	25.0	1.0	0.0	0
Author's dystro. adip. gen., case 2	15,400	78	18.0	2.0	1.0	0	18,200	82	16.0	1.0	0.0	1

Csépai found in one case of acromegaly, in another of dystrophia adiposogenitalis and in another case of myxedema, in all of which the conjunctival reaction was prolonged, no increase in the blood-pressure following the subcutaneous test. Our experience was quite different to this, however, as our three cases of prolonged conjunctival reaction showed a slight systolic increase of 10 to 14 mm., a figure, it is true, slightly below our normal controls, but not strikingly so. Further, two of the three cases with a normal conjunctival reaction showed either a very slight increase of 2 mm. or a very definite one of 28 mm. The third case, with normal conjunctival reaction, had an actual fall of 14 mm. of systolic pressure, a phenomenon which we are at a loss to explain, unless we can assign it to a faulty sample of adrenalin, as the two normal controls which received the same solution gave only a very slight increase in systolic pressure, namely, 6 and 8 mm.

Further, Falta[3] has pointed out that the subcutaneous administration of adrenalin causes a distinct leukocytosis, with an increase in the neutrophiles at the expense of the mononuclear and eosinophilic cells. We have applied this test to twelve normal controls (see Table II) and noted a varying degree of leukocytosis in eight patients with an average increase of 1180 cells per cubic millimeter, due to a slight increase in the neutrophiles and a corresponding decrease in the mononuclears and eosinophiles. However, in four equally normal patients, as far as the endocrine glands was concerned, there was a decrease in the total white cells, averaging 1200 cells per cubic millimeter, with little or no change in the leukocytic formula.

This test was first applied by Csépai to his hypophyseal cases, in which he found either no increase or at the most a slight increase in the total leukocytes, with, however, a slight relative increase of the neutrophiles at the expense of the mononuclears and to a less extent of the eosinophiles. Csépai therefore stated that any variation from the normal leukocytosis indicates disease of the ductless glands.

In our series there was only 1 case, and that after operation, which showed a distinct leukocytosis, of 3600 cells, with a slight increase of the neutrophiles and a corresponding decrease in mononuclears

and eosinophiles. In the other 5 cases there was either no leukocytosis or at the most a very slight one, with an average increase of 584 cells per cubic millimeter as compared with an increase in our 12 normal cases of 1180 cells, a difference we believe too small to be unduly emphasized. Further, there was no constant relationship between the effect of the adrenalin upon the blood-pressure and the effect upon the leukocytic formula.

The Conjunctival Pituitrin Test Csépai found that normally three drops of the commercial pituitrin as ordinarily used in obstetrical practice when instilled into the conjunctival sac cause no blanching or at the most only a very slight pallor, lasting ten minutes. These figures were the result of many observations by Csépai, though he does not state the exact number of patients tested.

We used twelve patients as normal controls (see Table I) and found no blanching, but rather reddening of the conjunctiva in 4 cases, a slight blanching of ten minutes' duration in 3 other cases, while in 5 others the blanching lasted from fifteen to twenty-five minutes. In other words, 7 gave a reaction within Csépia's normal limits, while in 5 it was prolonged and therefore pathological according to Csépai. He found in 2 cases of acromegaly a prolonged reaction (fifteen to twenty-five minutes), but a normal one in 1 case of acromegaly, 1 of dystrophia adiposogenitalis, 1 of Addison's disease, 1 of myxedema, 1 of Graves's disease and 1 of diabetes mellitus.

In our 3 cases of acromegaly the blanching lasted fifteen minutes in 2 cases and forty-five minutes in 1 case. The reaction was absent or at the most very slight in the secondary hyperpituitarism, and in both patients with dystrophia adiposogenitalis. We further cannot confirm Csépai's observation that when the adrenalin reaction was strongly positive the pituitrin was negative and conversely. We feel rather that the pituitrin conjunctival reaction is not as constant or as reliable as the adrenalin, and that many more controls in the normal and diseased states will be necessary before any reliance can be placed upon this test.

The Subcutaneous Pituitrin Test. Following Csépai's suggestion, the effect upon blood-pressure of the injection of 0.5 c.c. of pituitrin was observed. In 1914 he was not ready to publish

his own data. Therefore the twelve normal controls of our own series are the only ones available for comparison with our abnormal cases. (See Table I.) The blood-pressure, both systolic and diastolic, was read at ten-minute intervals for one hour. In the chart only the maximum systolic increase is recorded. This increase varied from 5 to 38 mm., or an average for 11 cases of 15 mm. One normal case showed a fall of 18 mm. without any apparent reason, as both the pathological case and the other normal control showed well-defined increases of the systolic pressure. In other words the increase of systolic pressure following 0.5 c.c. of pituitrin is very little less than that following 5 mgm. of adrenalin. Our 3 cases of acromegaly showed an average increase of 7, while the other 3 pituitary cases showed an average increase of 11 mm. in the systolic blood-pressure. There may be therefore a slighter response to subcutaneous pituitrin in patients with acromegaly than in the normal person, or even than in dystrophia adiposogenitalis and secondary hyperpituitarism.

The effect upon the leukocytes two hours after the injection was noted by us in 12 normal cases. (See Table III.) In 7 of the cases there was an average increase of 1128 cells, with a slight increase in the neutrophiles, but no change in the mononuclears or eosinophiles. In 5 cases, however, there was a distinct decrease in the total white cells, averaging 1380 cells, but again practically no change in the blood formula. In all 3 cases of acromegaly, as well as in the case of secondary hyperpituitarism and 1 case of dystrophia, there was a slight but definite decrease which averaged 500 cells per cubic millimeter. There was practically no change in the blood formula. In the case of dystrophia, with an associated pelvic cellulitis, there was a distinct leukocytosis.

Conclusions. 1. That a secondary hyperpituitarism may result from a greatly or rapidly increasing intracranial pressure as in Case IV of our series.

2. That the determination of a decrease in the sugar tolerance in the presence of other symptoms of disturbance of pituitary function justifies a diagnosis of increased activity of the pars intermedia.

TABLE III.—PITUITRIN SUBCUTANEOUSLY.

Diagnosis.	Blood picture before.						Blood picture two hours after.					
	Total W. B. C. per cu. mm.	P. N. per cent.	Ly. per cent.	Tr.andLM. per cent.	Eosin, per cent.	Mz., per cent.	Total W. B. C. per cu. mm.	P. N. per cent.	Ly. per cent.	Tr.andLM. per cent.	Eosin, per cent.	Mz. per cent.
Average 7 positive cases	+1,128	75	22	1	0.4	0.2	.....	76	23	1	0	0
Average 5 negative cases	−1,380	71	26	2	1.0	0.2	.....	71	26	2	1	0
Author's acromegaly, case 1	7,800	60	35	3	2.0	0.0	6,400	60	28	9	3	1
Author's acromegaly, case 2	5,800	69	26	5	0.0	0.0	5,700	73	23	2	1	0
Author's acromegaly, case 3	6,200	71	27	2	0.0	0.0	6,400	68	29	3	0	0
Author's hyperpituitarism	8,600	67	32	1	0.0	0.0	8,400	70	29	1	0	0
Author's dystro. adip. gen., case 1	5,900	64	34	2	0.0	0.0	4,900	68	32	0	0	0
Author's dystro. adip. gen., case 2	9,600	78	19	1	2.0	0.0	14,400	73	26	1	0	0

3. That the adrenalin conjunctival test may be of positive value in certain cases of dyspituitarism in demonstrating a hypofunction of the chromaffin system.

4. That the subcutaneous adrenalin test was only of doubtful value in both the normal and diseased cases studied by us.

5. That both the conjunctival and subcutaneous pituitrin tests were too equivocal to be depended upon for studying the functional activity of the hypophysis.

6. That the internal administration of the pituitary extract of either the whole gland or the anterior or the posterior lobes appears to exert no definite influence upon the symptomatology of the disease.

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CANCER OF THE PANCREAS

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The fact that several cases of cancer of the pancreas have recently come under my personal observation has been the incentive for presenting a brief clinical report on this comparatively rare disease.

Of 41,949 admissions to the medical wards of the Johns Hopkins Hospital up to June 13, 1919, there were 58 cases in which a clinical diagnosis of cancer of the pancreas was made. As the symptom-complex of pancreatic cancer is rather more definite than that in most of the diseases of the gland, it is very probable that the diagnosis in the great majority of these cases is correct. In order that there should be no possible error only 31 of these are included in this analysis, namely those in which the clinical diagnosis was substantiated by either autopsy or operation. Autopsies were obtained in 13, and in 18 the diagnosis was confirmed by operation alone.

Of these 31 cases, 29 were apparently primary cancers involving chiefly the head of the pancreas. In one instance the cancer was primary in the stomach, the pancreas having become invaded by direct extension. In the remaining case, the pancreas had become involved secondarily to primary carcinoma of the bile-ducts.

In most instances cancer of the pancreas is either of the adeno-carcinoma or scirrhus type, and in 12 of the 13 cases that came to autopsy these were the forms found to be present. In one of the autopsies performed by Sprunt the histological examination revealed an hemangio-endothelioma of the head of the gland. Fabozzi has described 5 cases in which he believed the cancer sprung from the Islands of Langerhans, but in this series no such instance was found.

Sex. Of the 31 cases, 22 were males and 9 females.

Age. From 31 to 40 inclusive there were 2 cases; 41 to 50, 15;

51 to 60, 9; 61 to 70, 6; and 71 to 80, 1. The largest number, 15, occurred in the fifth decade, the period of life when carcinoma is most common. The youngest case was in a man thirty-four years of age and the oldest in a man seventy-five.

Race. There was only one colored patient among the 31. As the proportion of colored to white admissions in the medical wards is about 1 to 7, this would seem to show a relative immunity of the colored race to cancer of the pancreas.

Symptomatology. A group of symptoms occur which, by processes of exclusion, enable us with a considerable degree of certainty to make a diagnosis of the existence of the disease. Among these, the most important are pain, jaundice of gradually increasing intensity, dilatation of the gall-bladder, a tumor mass, emaciation and symptoms referable to the shutting off of the pancreatic secretion from the intestinal tract.

1. *Pain.* This is often the earliest and most persistent of the various symptoms. It was present in 25 of the cases. It often increases in intensity with the progress of the disease. It is usually referred to the epigastrium radiating toward the back, shoulders or sternum. It may be located chiefly in the right hypochondrium when the head of the gland is chiefly involved. It has been ascribed by various writers to pressure of the growth on the celiac axis and its branches. When of an intermittent colicky character, it has been regarded as a true pancreatic colic, due to obstruction to the outflow of the pancreatic secretion resulting from compression of the pancreatic duct.

2. *Jaundice.* This is a very common symptom. It was present in 23 cases, absent in 6, and in 2 the records make no statement concerning it. It is often an early symptom and may be the first one to attract the patient's attention. Once established, it is persistent and often becomes intense. Since cancer usually involves the head of the gland, it is due to obstruction of the common duct by the tumor. If it appears suddenly it may be accompanied by colicky pain and cholelithiasis may be simulated.

3. *Tumor.* A palpable tumor was present in 12 cases. The mass is usually felt in the epigastrium when present and generally extends a little more to the right, owing to the more frequent involvement

of the head of the gland. Of Da Costa's 137 cases a tumor was palpable in only 13. The palpable mass may be lifted by the underlying aorta, and a systolic murmur may be heard over it owing to compression of the latter. Palpation is usually accompanied by a certain amount of sensitiveness.

4. *Emaciation.* Loss of weight, often rapid and extreme, is the rule. Emaciation was present in 29 of the 31 cases. While various factors contribute in its production, it is probable that the shutting off of the external pancreatic secretion from the intestinal tract, with resultant interference with fat digestion and absorption, plays an important part.

5. *Symptoms Referable to Shutting off of the External Secretion from the Intestinal Tract.* There was only one instance in which there was an actual *fatty diarrhea.* In 17 cases, however, the microscopic examination of the stools showed neutral fat globules or abundance of fatty acid crystals. Decidedly pale or clay-colored stools were noted in 22 of the 31 cases. Among 113 instances of carcinoma of the pancreas Mirallié found only 9 cases with *fatty stools.* One would naturally also expect disturbance of protein digestion in the intestinal tract, but Fitz found only 2 cases in which cancer of the pancreas was accompanied by disturbed digestion of proteins, as manifested by the presence of numerous undigested muscle fibers in the feces. When one considers how completely the common duct is obstructed in many of these cases, it is rather surprising that one does not more frequently find the large, bulky, fatty stools resulting from imperfect digestion of fats, proteins and carbohydrates, so characteristic of obstruction of the pancreatic duct by a calculus.

With more modern laboratory methods, T. R. Brown has shown us that the quantitative estimation of the stools for the various pancreatic enzymes, trypsin, steapsin and amylase is becoming of increasing value in determining the existence of pancreatic disease. Owing to the greater stability of the diastatic ferment, amylase, he believes that the quantitative estimation of the latter in the stools and urine is likely to prove of most value as a guide to disturbance of pancreatic function.

6. *Disturbance of the Internal Secretion.* With the extensive involvement of the gland frequently observed in cancer of the

pancreas one might expect to frequently meet with *glycosuria*. This, however, is not the case. Only 3 of the 31 cases showed the presence of sugar. In 1 case the quantity reached from 3 to 4 per cent. In all cases the glycosuria was of a mild type and intermittent. In no case was an acidosis present. Unfortunately, in no instance was a blood sugar determination recorded. In some of the reported statistics the percentage of cases of glycosuria have been higher. Among 50 cases Mirallié found glycosuria in 13. According to Opie, "The Islands of Langerhans persist within the stroma of the new growth and prevent glycosuria until destruction of the gland is far advanced. The glycosuria of pancreatic cancer disappears before death."

7. *Distention of the Gall-bladder.* This occurred in 21 of the 31 cases and is undoubtedly an important diagnostic sign. The gall-bladder was found ruptured in one of the cases. In the study of a considerable number of cases of obstruction of the common bile-duct from various causes, Courvoisier found that with obstruction due to biliary calculi the gall-bladder is usually contracted, while with occlusion from other causes the gall-bladder is generally distended. This is known as "*Courvoisier's law.*" According to Opie, the probable explanation for this difference is that contraction of the gall-bladder with biliary calculi is due to inflammatory changes, whereas, with obstruction due to carcinoma of the pancreas or other causes, inflammation is usually absent and the thin walls of the gall-bladder permit it to become distended.

The statistics collected by Ecklin substantiate Courvoisier's law. Of 172 cases of obstruction of the common bile-duct due to gall-stones, the gall-bladder was contracted in 110, normal in 34, and dilated in 28 cases; whereas, among 139 instances in which the common bile-duct was obstructed by other causes, the gall-bladder was contracted in only 9, normal in 9, and dilated in 121 cases. Among 61 of these cases constriction of the common bile-duct was due to carcinoma of the pancreas, and the gall-bladder was dilated in 58 instances.

8. *Enlargement of the Liver* The liver was enlarged in 12 of the 31 cases and this, with one exception, was not due to liver metastases. The opinions of various writers differ on this point. Bard and

Pic attached considerable importance to absence of enlargement of the liver in carcinoma of the pancreas. Mirallié, on the other hand, found the liver enlarged in 8 cases. The explanation, when such enlargement occurs, is not clear. It may in some way be connected with the jaundice and biliary retention.

9. *Vomiting.* This symptom was noted in 10 cases. It may be due to pressure of the carcinoma on the pylorus or duodenum, causing obstructive symptoms. The tumor may actually invade these portions of the gastro-intestinal tract and cause symptoms simulating primary carcinoma of these organs. There may be marked anorexia, whether vomiting occurs or not.

10. *Edema.* Swelling of the lower extremities occurred in 5 instances. A possible explanation of this may have been pressure on the inferior vena cava, which has been described in some cases. In this series it was not due to renal or cardiac disease.

11. *Fever.* The general statement is that carcinoma of the pancreas is unaccompanied by fever and when present it is usually attributed to some complication. In 13 of the series fever of a moderate and intermittent type was present. In 1 case the patient had suffered a chill during the course of the disease. In only one instance was there an accompanying cholelithiasis.

12. *Ascites.* There was free fluid in the peritoneal cavity in 4 cases. As well as could be determined this was a pressure manifestation. When present the ascites has usually been due to pressure on the portal vein. Of 113 cases of primary carcinoma of the pancreas collected by Mirallié ascites was present in 13. Cases with chylous ascites presumably due to rupture of the thoracic duct have been described.

Diagnosis. The recognition of cancer of the pancreas is not always a simple matter. In a considerable percentage of the cases, however, a group of symptoms occur which enable one to make a diagnosis with a reasonable degree of certainty. The features of chief importance are epigastric pain, persistent jaundice of gradually increasing intensity, a distended gall-bladder, an epigastric tumor, and progressive emaciation and cachexia. If a tumor be not palpable and if jaundice be absent, which may be the case if the cancer be in the body or tail of the gland, a clinical diagnosis is almost

impossible. Symptoms referable to disturbance of the internal and external secretion of the pancreas may point toward a lesion of the gland, but are of less value.

Cholelithiasis is the disease that is most likely to simulate carcinoma of the pancreas, especially if there be a stone in the common duct. Here, however, the attacks of pain are more likely to be colicky in character and the jaundice is usually more abrupt in its onset and is intermittent. There are likely to be chills and fever—the so-called Charcot's hepatic intermittent fever. As a rule the gall-bladder is not palpable. If the gall-stone be impacted in the common-duct the jaundice may be intense and persistent and the differential diagnosis may be very difficult. In carcinoma of the pancreas the pain is less colicky, the jaundice is more gradual in its onset, is persistent and becomes very intense. The gall-bladder is frequently dilated and chills and fever are very infrequent. The presence of a palpable epigastric tumor, with the above symptoms, would strongly point toward pancreatic cancer.

Jaundice resulting from *carcinoma of the liver, bile passages, duodenum, or stomach, compressing the common bile-duct*, has the gradual onset and progressive character seen in carcinoma of the pancreas, but emaciation and weakness usually progress less rapidly. The diagnosis between primary carcinoma of the pancreas and malignant disease arising from the common bile-duct or duodenum is almost impossible.

Treatment. The medical treatment is most unsatisfactory, is essentially palliative, and is directed toward the relief of pain, improvement of intestinal digestion, and combating any associated glycosuria. Owing to the obstruction to the flow of the pancreatic juice into the intestinal tract, with the marked emaciation resulting from interference with fat and protein digestion, some benefit may accrue from the administration of 0.3 to 0.6 grams (5 to 10 grains) of commercial pancreatin, which contains both trypsin and steapsin.

Operative treatment, as might be expected, has been most unsatisfactory and is scarcely to be recommended. Of 13 cases collected by Körte and Robson, and quoted by Opie, 5 died as the immediate result of the operation, and 5 succumbed within from a few weeks to five months after the operation.

Where life is made almost intolerable from the itching due to the intense jaundice, a cholecystenterostomy or a biliary fistula operation may be contemplated. In several instances where the former operation has been performed the patient has lived from sixteen to eighteen months, with some evidence of at least temporary improvement and with considerable relief from the distressing pruritus.

Summary. Carcinoma of the pancreas, confirmed by autopsy or operation or both, occurred in 31 cases among the first 41,949 patients admitted to the medical wards of the Johns Hopkins Hospital. In 29 of these the disease was primary in the gland. Of the 31 cases, 22 were males and 9 females. The largest number, 15, occurred in the fifth decade, viz., from forty-one to fifty years of age. Only 1 occurred in the colored race.

The most important symptoms and signs in arriving at a correct diagnosis occurred as follows: Pain in 25; persistent and increasing jaundice in 23; palpable tumor in 12; distended gall-bladder in 21; emaciation and cachexia in 29; neutral fat and fatty acid crystals in the feces in 17.

Other features of interest occurred as follows: Vomiting in 5; edema of the feet and ankles in 5; ascites in 4; enlargement of the liver in 12; intermittent glycosuria in 3; acholic stools in 22.

Gall-stones of the common-duct, and carcinoma of the liver, bile-passages, duodenum or stomach, compressing the common-duct with resultant jaundice, are the conditions from which carcinoma of the pancreas has chiefly to be differentiated.

The treatment is practically hopeless and chiefly palliative. Pancreatin preparations may aid intestinal digestion and help to lessen the severe emaciation. Cholecystenterostomy or production of a biliary fistula may be considered as a possible means of relieving the intolerable pruritus due to the intense jaundice.

THE AUTOPSY SERVICE OF THE AMERICAN EXPEDITIONARY FORCES

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THE technical work of the Laboratory Section of the Division of Laboratories and Infectious Diseases was so modified by the stages of developmental organization and by the incidence of epidemics and hostilities that it may be divided roughly into four periods:

1. From the landing of troops, June 10, 1917, to November 30, 1917, about which date a large number of cases of pneumonia developed.

2. From December 1, 1917, to May 31, 1918, when the hospitals of the A. E. F. began to be concerned most actively with wounded soldiers following the heavy German offensive of May 28.

3. From June 1, 1918, to November 30, 1918, the period of serious epidemics and of greatest battle activity, during which time the laboratory was concerned largely with cases of enteric disease, influenza, and with recently wounded patients.

4. The period of demobilization from December 1, 1918, to May 15, 1919.

A study of the distribution of the autopsy service by periods and in the several types of hospitals in the A. E. F. shows the following:

During the first period, to November 30, 1917, very few postmortems were made in the A. E. F. The clinical service was extremely light, the attending medical officers and surgeons had time to study their cases with great care, and thus, even of the few patients who did die, the necessity for a postmortem examination had not pressed itself on the attention of the attending officers. Of

the postmortems that were made, either incomplete records were kept or those that were kept were in some instances lost, so that there remain for the period but fourteen protocols in all which have been received in the Office of the Director of the Division of Laboratories. Most of these autopsies were made at Army Laboratory No. 1, Naval Base Hospital No. 1, and Camp Hospital No 33. These autopsies represent less than 25 per cent. of the deaths which occurred during the period.

During the second period, December 1, 1917 to May 31, 1918, though the conditions for the leisurely study of patients by clinicians and surgeons still continued, the latter had come to realize their difficulties in diagnosis and treatment and pathologists themselves had begun to take more interest in their work; thus autopsies increased in May to 57 per cent. of the total number of deaths in the hospital. The percentage increase in April and May was further due to the fact that, April 2, Circular No. 17 was issued from the Chief Surgeon's Office, the first paragraph of which read as follows:

1. *Autopsies are authorized in all cases of officers and soldiers and should be performed whenever possible. These autopsies shall be performed only by medical officers or authorized assistants. At the conclusion of the autopsy the body must be restored, as far as possible, to its original form.*

Though by the end of May, 1918, the beginning of the third period, there were in the A. E. F. seventy-two hospitals and laboratories, there were less than fifteen pathologists capable of making postmortems and intelligently interpreting the results. This condition was due in part to the long neglect of autopsies in many civil institutions in the United States, with the inevitable reduction in the number of pathologists, and in part to the overshadowing status of bacteriology in military laboratories. The autopsy service in the Army in the United States had not been established as a routine procedure, but, on the contrary, autopsies were made only on the written authority of the commanding officer of the hospital. However, in the A. E. F. the need of a routine autopsy service, amounting in fact to professional inspection of the diagnostic and therapeutic measures of medical and surgical officers, became rapidly apparent during the summer of 1918. Surgeons were called upon to diagnose

and treat, with little time for study or reflection, many gunshot wounds with the like of which they had had little or no previous experience. Even those who were well grounded in the general principles of surgery were forced to make decisions and institute treatment thereon without sufficient basis or study. As a result, there were errors in diagnosis and errors in treatment. The worst of these could be determined only by the pathologist. In like manner, attending medical officers, that is, in cases of war gas poisoning and especially in the widespread epidemic of influenza and pneumonia, were brought face to face with conditions with which they were totally unfamiliar, and were frequently forced to make diagnoses and institute treatment with a very meager knowledge of the facts. Here autopsies were of tremendous importance in securing for the attending man a knowledge of the pathologic lesions, which knowledge he could use in his diagnosis and treatment of subsequent cases. When, late in the fall of 1918, and the winter of 1919, the fourth period, numerous isolated epidemics of typhoid fever in vaccinated troops began to appear, the conditions were in many instances so obscure that the clinicians failed to make the diagnoses, the pathologist being the first to recognize the true nature of the disease when the patient came to the autopsy table.

Looking forward to some such possibility as occurred, the Director of the Division of Laboratories, in June, 1918, requested that ten competent pathologists be cabled for from the United States in addition to those coming over with hospital organizations. These arrived in due time and, being placed advantageously, assisted materially in improving the service. In addition the activities in forward areas were covered to better advantage by dividing the territory into sectors and placing, at Baccarat, Toul, Souilly and Paris respectively, competent pathologists attached to an evacuation or base hospital therein, with orders to act as consultants for the surrounding areas. In addition to these measures, the importance of autopsies was brought to the attention of laboratory officers and commanding officers of hospital organizations personally by inspectors from the Office of the Director of the Division of Laboratories, by letters, and by indorsements on monthly reports. As a result, the autopsy service rapidly mounted and, though there

were never enough competent pathologists in the A. E. F. to cover the needs at all points, there being only about 200 pathologists out of 685 laboratory medical officers at the time of the signing of the armistice, the service mounted in August and September of 1918 to 92 per cent. of all deaths in hospitals with laboratories attached. In October the total number of autopsies reached 3896, though this was but 85 per cent. of the deaths in hospitals with laboratories attached, the autopsy service like every other being overwhelmed by the enormous number of deaths from influenza and the battle casualties of the Argonne offensive.

The distribution of autopsies among hospitals of the various types indicated where the stress for autopsy service came during the influenza epidemic and during battle activity. The greatest mortality was of course in the base hospitals. It is worthy of note that after July, 1918, many more autopsies were done in camp hospitals than in evacuation and mobile hospitals. This was owing to the greater number of camp hospitals and to the fact that many of them actually functioned as base hospitals. The lesson to be drawn from this experience is that competent pathologists should be provided for these organizations as well as for base, evacuation, and mobile hospitals. On the other hand, it is doubtful whether conditions will ever warrant the performance of any considerable number of autopsies in filled hospitals by personnel attached permanently thereto. Here it is believed the necessary study of battle casualties, particularly of gas poisoning, can best be done, as in the French service, by centrally located laboratory officers provided with motor transportation for the rapid concentration at any point where gas casualties have occurred. This plan was attempted in the A. E. F., but for the most part failed for lack of transportation

The general quality of the autopsies, in so far as their main object was concerned—namely, obtaining data for the immediate information of the attending physician and surgeon—was very high. This is especially true when it is remembered that, under the usual conditions under which both physician and surgeon were working, neither had any time to consider minute details of questionable importance. On the other hand, there were so many gross errors both in diagnosis and treatment, which were of such unquestionably vital importance

in the care of the sick and wounded subsequently coming under observation, that in many instances it required only the opening of the body to enable the merest tyro in morbid anatomy to demonstrate them to the attending medical officer. In most instances the attending physician or surgeon was keenly alive to the benefit to the case of tomorrow to be derived from these observations. Now and then a cock-sure physician or surgeon ignored the findings of the pathologist until it became necessary to force them upon him. Here and there the commanding officer of a hospital, usually in a forward area under the stress of a huge inflow of battle casualties, failed to recognize the importance of the pathologist's inspection of the other professional services and placed his laboratory officer in charge of supplies or the mess, to the serious detriment of the diagnosis and treatment of the sick and wounded. There can be no question but that the uncontrolled surgery under such circumstances did great harm, which might have been obviated had the pathologist been permitted to exercise his proper functions and point out to the surgeon the gross blunders the latter was repeatedly making.

Judged from the standpoint of records for subsequent scientific study, the autopsy service was of very varied character. Only a relatively small proportion of laboratory officers had had an adequate preparation in the interpretation of lesions at the postmortem table, and, of these, still fewer had been properly trained in accurately recording their observations. Trained clerical assistants and typewriters were almost unobtainable. The records of some of the very good men are exceedingly meager. In times of great stress this was true of everyone. Even one of the best pathologists, who made twenty-two postmortems in one day, of course left records of only the most essential facts. The incidence of tuberculosis other than as a cause of death was routinely recorded by but five pathologists, who made any considerable number of autopsies. But as one goes through the 15,000 protocols which have been received in the Office of the Director of the Division of Laboratories and remembers the conditions under which most of the pathologists worked for a large portion of the busiest time, one is struck with the high quality of the work from a large number of the officers, many of whom pre-

viously had very meager autopsy experience. The officers in charge of the analyses of these protocols say they are convinced the quality of the records will compare most favorably with any consecutive series of similar size from any civil hospital or hospitals in the United States. This is of course due in part to the relatively narrow limits of age, sex, time, and disease variation.

Early in July the recording and cross-indexing of autopsy protocols was begun in the Office of the Director of the Division of Laboratories. Inadequate assistance rendered progress in this direction very slow, however. After the signing of the armistice, the release from duty elsewhere of a few competent pathologists made it possible to place the analyses of the autopsy protocols concerning a few diseases on a better basis. In order to facilitate the work in the Central Office and to obtain the benefit of the review by the competent pathologists scattered throughout the A. E. F., three office letters concerning respectively influenza and pneumonia, gunshot injuries, and war gas poisoning, were sent out to laboratory officers selected because of their ability and experience. These office letters gave forms for the analysis by the laboratory officer of all cases coming to autopsy under his individual observation. On the receipt of these analyses in the Office of the Director, they were compiled and coördinated with each other and with scattered protocols from other laboratories. Two other compilations are in progress, one on typhoid fever and another on tuberculosis. It is believed that all of these will be of immediate military value. In addition to these, however, the other autopsy protocols contain a great wealth of data for subsequent study, that is, of meningitis, dysenteries, cardiovascular lesions, and so forth.

One field of postmortem examinations which might have yielded invaluable results from the purely military standpoint was entered by but one pathologist in the A. E. F. This was the examination of the bodies of soldiers killed in battle. This service does not necessitate the making of autopsies but only a study of the site and character of immediately fatal injuries by competent medical officers with a good knowledge of anatomy and some appreciation of the character and effects of missiles. Where conditions will permit, a careful investigation of the battle dead in all of the different types

of combat activity should yield information of inestimable value in both offensive and defensive warfare. The effectiveness or ineffectiveness of the many types of small arms missiles alone has been made the subject of but very little investigation with human targets under battle conditions. Until such a study can be made extensively and the observations collected and analyzed, the relative effectiveness of offensive warfare with small arms, hand grenades, shell fire, poison gases, and so forth, rests upon very incomplete and inaccurate observations and must remain largely a matter of conjecture. Similarly, without such studies, all attempts at the provision of armor which avoids, on the one hand, unnecessary weight and extent, and, on the other, penetrability, are proceeding without what would seem to be absolutely essential information of combat results. Such information could readily be obtained during battle activity by temporarily attaching competent medical officers to burial parties.

In plans for the autopsy service in the future the general principle should be followed that, whenever men die after having been made the subject of diagnosis or treatment, their bodies should be examined postmortem by competent pathologists. This policy of inspection of the services of the medical and surgical departments will furnish the greatest possible safeguard for the thoroughness and accuracy of their work. Of course such a policy presupposes a large number of well-trained pathologists, and there is no way for men to obtain such training except by more general autopsy examinations in civil hospitals. Provision should also be made for the better correlation of pathologic work with that of the clinical services both in civil practice and under military conditions. Only by the most perfect liaison between these services can the sick and wounded receive proper diagnosis and treatment.

A ROENTGEN RAY SIGN OF PERINEPHRITIC ABSCESS.

By M. H. FUSSELL, M.D., and H. K. PANCOAST, M.D.

During the study of Case II in this report a curious fluoroscopic finding was observed which directly led to a diagnsois of perinephritic abscess, and which was confirmed by operation. The same fluoroscopic sign was noted in Case I, but in this particular case the diagnosis was certain before the fluoroscopic finding was seen, hence no particular attention was paid to it except to note its presence. So far as either of us can discover this roentgen-ray finding has not been previously reported, though, of course, in the mass of literature a notice of it may easily have been overlooked.

Case I.—F. H. W., male, aged thirty years, was admitted to the University Hospital, under the care of Dr. J. B. Carnett, October 2, 1916, with a diagnosis of renal calculus on the left side. The diagnosis was confirmed by roentgen rays and the stones removed by Dr. Carnett. The patient did well until October 10, when he developed fever of a mild type. On October 25 the fever became septic in type and continued until December 13, when a fluoroscopic examination showed fluid at the seat of the operation. This fluid was demonstrated while the patient was standing in the fluoroscope. The shoulders of the patient were grasped and the patient's body moved quickly two or three times from side to side. Watching the fluoroscopic picture showed a distinct wave in the supposed fluid. This observation was made by Dr. Pancoast. He offered the explanation that a collection of fluid was around the kidney, which showed the wave when agitated. The renal region was opened and a huge sac of pus demonstrated within the capsule of the kidney.

No other opportunity was given to discover whether this sign was an accidental one or whether it was common in subdia-

phragmatic collections about the kidney on the left side until Case II was seen.

Case II.—A. F., male, aged forty-six years, was seen with Dr. Shelly, of Ambler, Pa., May 14, 1918. The patient had been sick three weeks, was tired and chilly, and had fever of a septic type. He had pain referred to the base of the left lung. A paracentesis had been performed by Dr. Shelly, who had removed 3 or 4 c.c. of clear fluid with a needle from the base of the left chest. When seen by the writer there was pain and tenderness over the region of the left kidney, but nothing else could be detected. A needle was inserted in the left chest, but the tap was dry.

In the history which was obtained there were symptoms indicative of what was thought to be a peptic ulcer; a tentative diagnosis was made of subdiaphragmatic abscess from a perforating ulcer. He was sent to the University Hospital for a roentgen examination, but this was negative, and he returned the same day.

In a week after this, his symptoms still continuing, he was again sent to the hospital for careful observation. The symptoms were an irregular fever of septic type, with persistent but slight pain over the region of the left kidney. A roentgen-ray examination, with the patient lying on his back, showed the diaphragm to have the normal arch, and nothing particular could be seen. A plate taken, however, showed a beautiful picture of gall-stones, but did not reveal the presence of liquid. Remembering the experience with Case I, the patient was placed upright in the fluoroscope and the first observation was that the left leaf of the diaphragm was flat and was immobile, and had lost its normal arched position.

The patient's shoulders and body were then moved quickly from side to side, and there was distinctly seen the same wave above the renal region which was observed in Case I. This observation was confirmed by both authors and by several other observers.

In view of these facts an exploration was advised in the left lumbar region, with the belief that all of the symptoms were due to a collection of pus in or around the left kidney.

Dr. A. C. Wood, who performed the operation, hesitated to explore the region because the local physical signs of a collection in that region were so slight, but urged that the gall-stones be removed and

the lesser peritoneal cavity be explored. This, of course, was a rational opinion, but because of the curious fluoroscopic sign he was persuaded to open the kidney region. The incision showed the left kidney tightly bound down by its lower half. But surrounding the upper pole an abscess containing approximately 200 to 300 c.c. of pus was found.

The patient made an uninterrupted recovery and was discharged June 25.

On October 30 the patient developed marked symptoms of gall-bladder disease. He was again roentgenographed and the first plates showing gall-stones were confirmed. The gall-bladder was removed and showed thirteen stones. There was no evidence of previous or present collection of pus in the lesser peritoneal cavity. Today the patient is well.

This fluoroscopic sign is reported, because we believe it will be of value in certain obscure cases of fever, with suspicious signs about the left kidney, but which signs are not certain enough to warrant an exploration.

In Case I it will be noted the pus was within the capsule of the kidney; no note was made as to the shape of the diaphragm. In Case II the diaphragm had an entirely normal appearance when the patient was lying down and became flattened when the patient was upright. This phenomenon is not clear to us. We have thought of many explanations, but none seem satisfactory. It will be noted also that the amount of fluid was not large, which makes the sign of value in early cases. This second patient was soon relieved, having been in the hospital only about four weeks after operation.

Of necessity, pus about the right kidney will not be expected to give this sign, as the liver intervenes between the kidney and the diaphragm. So far as we know no such observations of collections of pus between the liver and the diaphragm have been made.

It is confidently hoped that other observers will search for the presence of a wave under the diaphragm in cases of subdiaphragmatic or perinephric abscess when the body is quickly moved from side to side.

TRENCH NEPHRITIS AT A BRITISH GENERAL HOSPITAL IN FRANCE

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"Trench nephritis" is best defined as a type of nephritis occurring among soldiers and characterized by the frequent presence of bronchitis and dyspnea, the suddenness of onset of such uremic manifestations as convulsions, the rapid subsidence of well-marked renal dropsy, the rarity of occurrence of inflammatory complications and by an extraordinarily low mortality.

In 1917 and 1918 the disease was common. It represented about 5 per cent. of all medical casualties occurring in two different British general hospitals during these years, and was far more frequent than any acute type of nephritis seen in civilian hospitals. While the disease affected soldiers of all ages and of varying lengths of war experience, it seemed to be most common in men between the ages of thirty and forty who had been in France less than six months. An attempt was made to discover epidemic foci of the disease by tracing the patients in this series to their original position in the line. The result was negative. Trench nephritis seemed to be diffused through an immense number of men in France who were occupying a wide territory.

It was desirable to make as careful a clinical study of the disease as was possible under the circumstances, therefore it seemed preferable to observe a few typical cases thoroughly for a reasonable length of time rather than to obtain single facts of any sort on numerous patients who were evacuated quickly. Accordingly, twenty-two cases were selected because of their apparent severity from all nephritic patients admitted and were retained in hospital

from two to eight weeks. Though the cases studied were few in number, they seemed typical of the disease as it has been described. Nineteen cases at entry gave a history of less than two weeks' duration, and of these one had been ill one day. No cases showed signs of having preëxistent chronic nephritis. Nineteen cases had well-marked dyspnea or orthopnea at entry. Four cases had a sudden attack or repeated attacks of epileptiform convulsions simulating uremia. Twenty-one cases entered with definite edema. None of the cases had inflammatory complications and none died of nephritis.

While the dyspnea was a striking characteristic of the disease it was not caused by acidosis. It was true that slight acidosis as measured by Van Slyke's method was not uncommon in the type of nephritis observed, though the cases with the severest dyspnea did not necessarily have the greatest acidosis, nor did the latter cease as the shortness of breath improved. Probably the acidosis observed was similar to that which has been described in chronic nephritis, and was referable to an impermeable kidney rather than to any essential overproduction of acids within the body.

The four cases with convulsions were striking in intensity and apparent severity. All developed this complication within a day of entry to the hospital after a fatiguing journey of considerable length and exposure. Three of the cases entered with a systolic blood-pressure of at least 170. While other non-convulsive cases were seen with an equally high blood-pressure, and one occurred with a lower blood-pressure, the association between hypertension and convulsions was noteworthy. None of the cases showed a significant acidosis or accumulation of blood-urea with a much lowered urea-index. All showed impairment in the twenty-four-hour excretion of sodium chloride, which was followed by an excessive excretion, suggesting that chloride retention was a feature common to all. From these observations it did not seem probable that the convulsions were "uremic" in the ordinary sense. It is possible that some cerebral circulatory disturbance or localized edema was the underlying cause.

As the nephritis subsided each case showed a general form of change in kidney functions. After a variable period of rest the

blood-pressure, which was usually elevated at first, returned to normal. The water excretion rose, sometimes promptly, sometimes slowly, and the edema vanished. Coincidentally chlorides were excreted in large amounts. In the severest cases, the blood-urea was much increased and the urea index was lowered. As the condition improved the blood-urea concentration fell toward normal and the urea index rose. There was no obvious relationship between the increased blood-pressure, edema and the amount of urea in the blood. An interesting phenomenon was the characteristic excretion of albumin. At first it was excreted in large amounts. As the nephritis improved the excretion of albumin increased and eventually disappeared. This suggested an exudative process in the kidney, increasing as the lesion began to heal and disappearing with recovery. The sediment at first contained granular casts, cellular debris and variable amounts of blood. Later hyaline casts appeared. Finally the sediment became normal except for the persistence of a rare hyaline cast and an occasional blood corpuscle. This course suggested nothing specific in the nature of the nephritis as judged by usual methods of studying kidney disease.

The cause of the disease was not determined, though there was a certain amount of evidence for believing that it was of infectious origin and possibly related to trench fever. The majority of cases entered with fever, which became normal within a few days. Certain cases relapsed and two types of relapse were met with. The first was associated with no demonstrable change in kidney function but with a "spiked" rise in temperature, accompanied by shin pains, characteristic of trench fever. The second was associated with a "spiked" rise in temperature and with definite change in kidney function, without any shin pains. The excretion of water and chloride diminished, there was a rise in the blood-urea and a fall in the urea-index, the excretion of albumin diminished and later increased when renal function improved.

As a result of the information obtained by corresponding with the patients in this series at intervals up to eighteen months after discharge from hospital the prognosis of "trench nephritis" seemed good. One case died of influenza but no autopsy was made. Six cases recovered and were back in France. The others were still

in hospital or had been discharged from the army as unfit. However, their histories suggested that they were slowly improving, and there was no evidence from their own feelings or the few medical opinions that could be obtained that the disease had developed into a chronic progressive nephritis.

On the whole, "trench nephritis" appeared to be an acute type of nephritis common among soldiers in the recent war. It was probably of infectious origin and possibly related in some manner to trench fever. It was a mild type of nephritis in regard to mortality and the prognosis in regard to ultimate cure seemed good, although cases will have to be followed for several years before this statement can be proved.

The changes in kidney function which were observed were in no way specific for this type of nephritis, but characteristic of acute nephritis in any form. The dyspnea was not due to acidosis. The convulsions observed were not "uremic" in the ordinary sense, but were probably due to cerebral edema or to cerebral circulatory changes. The general anasarca was intimately related to chloride retention. The severest cases had marked urea retention. Chloride retention, hypertension and urea retention seemed independent of each other. The most striking features of the disease were its frequency and the rapidity with which it cleared up under a simple routine form of treatment.

AN EXPERIMENTAL STUDY UPON THE IMPREGNATION OF CLOTH WITH PEDICULICIDE SUBSTANCES[1]

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MINNEAPOLIS, MINN.

The problem of freeing the soldiers from lice divides itself into two distinct phases: (1) The laundering and bathing procedures for ridding the clothes and the men of lice or eggs already present. These were possible only behind the lines. (2) The use of sachet powders and impregnation of clothes and underwear with substances which would kill or prevent the growth or even the presence of lice in the clothing. Since in many cases the soldiers were on duty continuously without change of clothing for three weeks or more this phase of the problem assumed particular importance.

In spite of the very large number of researches, which reaches into the hundreds, that have been published or kept as confidential reports of the various governments since the beginning of the war, many difficulties have remained to be overcome, and it was to aid in this that the present series was undertaken, at first under a research fund grant from the Regents of the University of Minnesota and later under the auspices of the Medical Science Division of the National Research Council. The researches upon the growing and breeding of lice, as well as upon conditions governing the laundering and ironing of clothing and the compounding of various sachet

[1] This research was aided in part by a Research Grant from the Regents of the University of Minnesota and in part by a grant from the Division of the Medical Sciences of the National Research Council, who have given permission for the publication of the report.

powders, as well as a preliminary publication on the testing of a considerable number of substances used in the impregnation of cloth, have already been published by one of us (M.)[1] and are not a part of the present paper. The entire study is now in press as a University of Minnesota monograph under our joint authorship and the detailed publication will soon appear.

This method at first employed in this research was to spread 1 gram of the substance to be tested upon a piece of cloth such as is used in the soldier's underwear 6 x 8 cm. in size, allow the substance to evaporate, and to test the duration of its power to kill lice by cutting off small strips at intervals and placing such a strip in a glass vessel in which a number of lice and eggs were kept. The vessel was then kept at incubator temperature and the percentage of the lice which were alive after twelve-hour intervals was noted, as well as the ability of the various batches of eggs to hatch out.

In order to be regarded as effectual the substance being tested had to kill 80 per cent. of the lice within twelve hours, of 100 per cent. in twenty-four hours.

All the lice were fed daily or twice daily upon the forearms of human subjects by Moore and a corps of assistants. That this was no indifferent procedure was shown by the fact that each of the persons doing so suffered more or less from fever, rash and glandular enlargement, and a condition somewhat resembling but not identical with trench fever, which has been described by Moore[2] in an article in the *Journal of the American Medical Association* and by both of us in an article in the *Archives of Internal Medicine*. The testing of the substances upon the louse was all done by Moore, the chemical syntheses by Hirschfelder.

The mere evaporation of the substances from the cloth exposed to the air was soon found not to coincide entirely with the disappearance of the substance when worn next to the skin, and accordingly simple evaporation was discarded as a criterion, and in the present research the substances were tested entirely by wearing a patch of impregnated cloth 6 x 8 cm. pinned to the undershirt and in contact

[1] W. Moore: Jour. Am. Med. Assn., 1918, vol. lxxi, 530.

[2] Jour. Am. Med. Assn., 1918, 71, 1481. A. D. Hirschfelder and W. Moore: Arch. Int. Med., 1919, vol. xxiii. 419.

with the skin of the wearer. These gave a fair indication of the conditions under which the substances would be used in practice, and it was also possible to determine from the presence of reddening of the skin under the patch whether the compounds were too irritating to be used.

In the preliminary paper referred to above Moore has described the effects of impregnating the cloth with various lubricating oils, lard oil, fish oil, bone oil, and with various vegetable oils such as cotton-seed oil, rape-seed oil and palm oil.

These were effective only in concentrations that would render the clothing so saturated with oil that they could not be worn, and were only slightly effective when 1 c.c. to 8 square inches, enough to make the clothing visibly oily, was used.

Organic acids (salicylic, oleic, valeric) were useless; thymol iodide failed to kill; phenyl iodide was transitory. Pure anthracene was useless, but crude anthracene killed for 118 hours.

The metallic salts, copper oleate, zinc sterate, zinc chloride, ferrous sulphate, sodium arsenate in 2 per cent solution and saturated lead acetate gave negative results, but saturated $HgCl_2$ killed.

Sulphur was negative. Iodoform which had been used effectively by the British in the N. C. 1 (naphthalene, creosote and iodoform, 96 per cent. naphthalene, 2 per cent. each of others) sachet powders was of some value, but the naphthalene killed only for twelve hours, though cloth impregnated with alphanaphthol retained its killing power for 360 hours and alphanaphthylamine for 720 after simple exposure to the air. On account of its toxicity the cloth was not worn, so that these figures are not comparable with the figures given when the cloth was worn.

Orthonitranilin, which lasted 480, is too toxic to man to admit of its use. Heliotropin was found to have retained its killing power after exposure to the air for 528 hours, but on being worn lost it after twenty-four hours, although if mixed with cocoa butter it lasted for 168 hours. This was due to the crystallizing.

The success of British investigators with naphthalene and creosote powders and our own results with cresol indicated that cresol was about the most useful substance, but that it disappeared from the clothing too rapidly to suit the purpose. It was accordingly

suggested by one of us (H.) that derivatives of cresol preserving the general cresol structure but diminishing the volatility might afford the solution of the problem, and on this account a number of cresol derivatives were synthesized.

After methylene dicresol, cresyl benzoate and the cresyl phosphates and a mixture of dicresyl-ethers and cresyl ketone were found to be ineffective, a systematic study of the halogenated cresols was undertaken. Attempts made to prepare these by most of the methods described in Beilstein's *Handbuch* gave unsatisfactory results, but satisfactory bromination could be secured by using Koppeschaar's mixture of sodium bromate, sodium bromide and hydrochloric acid.

Much better results were secured, however, by a method suggested by Dr. W. H. Hunter dropping the calculated amount of bromine from a separating funnel directly into glacial acetic acid containing the cresol and a small piece of bright iron wire as a catalyzer. Bromination as shown by titrating a sample with KI and thiosulphate was complete in less than an hour. The mixture was then neutralized, separated and filtered off, washed first with sodium thiosulphate to remove excess of bromine or bromine that had entered the hydroxyl group, then with sodium bicarbonate and water, and finally filtered or separated off.

Chlorine was introduced by bubbling into the glacial acetic acid solution of cresol in the presence of iron wire until the calculated weight of Cl had been taken up. The substances were otherwise treated in the same way as the bromine derivatives.

Iodine was introduced in saturated sodium bicarbonate solution in the presence of potassium iodide. A series of mono- and dibrominated chlorinated and iodo orthometa and paracresols was thus prepared in which the halogen had entered the ring. By this mode of treatment the trihalogen compounds of the metacresol only is formed and no trihalogenated ortho and para compounds were obtained.

Chlorine was also introduced into monobrominated metacresol and in this way a monobrommonochlor and a monobromdichlor metacresol was formed and in the same way a dibrommonochlor metacresol.

When patches of cloth impregnated with these substances were worn it was found that the monochlor orthocresol had no killing power after being worn twenty-four hours and that the dichlor orthocresol killed 100 per cent. after being worn twenty-four hours, but none after forty-eight hours.

The mono iodo orthocresol was variable and uncertain in its effect, but none of the samples killed more than 40 per cent. of the lice after being worn more than 168 hours. The monobrom para- and the monobrom metacresol lost their killing power after forty-eight hours, while the dibrom orthocresol retained it for 120 hours and the dibrom-metacresol for 240 hours. On the other hand, the tribrom metacresol possessed too low a volatility, and though lice were killed during the first twenty-four hours, probably on account of the presence of a lower brominated impurity, after thirty-six hours the killing power was completely lost.

Evidently the optimum volatility to secure the persistence of louse killing power lay with the dibrominated cresol. An attempt was therefore made to prepare chlorbrom cresols in order to see whether a still nearer approach to the optimum could be made.

The monochlor monobrom metacresol lost its killing power after forty-eight hours, and the monochloridibrom metacresol lost it after forty-eight, though it still killed 100 per cent. of the lice that were exposed to its action for thirty-six hours. The dichlormonobrom metacresol, however, preserved its killing power for 312 hours (thirteen days), thus representing the best compound of the series. This compound, which has not been described in literature, is a white crystalline compound with a melting-point of 62°. When beechwood creosote was treated with two molar parts of bromine a product was formed which still killed after 240 hours. Trieresol treated with bromine naturally forms a mixture of bromo-cresols probably ranging from the mono to the tribromcresol in varying amounts. When two molar parts of bromine were added and the mixture purified in the same way as the pure cresols the product possessed killing properties after having been worn for 96 hours. When three bromines were added it did so for 120 hours. A sodium salt of the dibrominated tricresol was prepared (by Moore) by treating with an excess of 3 per cent. NaOH. This compound

possessed a high killing power for 192 hours and a low but persistent killing power for 360 hours.

We have also studied the aluminum, magnesium, and calcium compounds of cresol, with a view to preparing insoluble compounds of the cresol derivatives which should be less alkaline than the sodium compounds and should slowly split off the cresol so as to continue its louse killing power. Though the compounds of magnesium and calcium with the halogenated cresols were not prepared, it seems probable that these would even be better suited than the sodium compounds for the purpose of the research. Since naphthaline was rated next to cresol, in the experience of the British, corresponding chlorinated naphthaline derivatives were prepared by the method described by Emil Fischer, but these were less efficient than were the cresol derivatives.

After this series was completed the dibromxylenol, the monobromcarvacrol and the dibromeugenol were prepared by Prof. R. A. Gortner.

Both the dibromxylenol and the monobromcarvacrol were much less volatile than the dibrom metacresol and killed just as rapidly. Dibromeugenol, which was even less volatile than the tribrommetacresol, killed within twenty hours while the tribrommetacresol failed to kill.

The effect of the monbromcarvacrol did not last any longer than that of the dibromcresol when worn, but the reasons for this were not determined.

The substances therefore which were found to be best suited to the purpose were the dibrom metacresol, which lasted ten days, and the dichlormonobrom metacresol, which lasted thirteen days; and these compounds seemed to fulfil the requisites of the problem as far as a laboratory trial could demonstrate.

Further pursuit of the problem was rendered unnecessary by the signing of the Armistice.

THE EARLY ROENTGEN DIAGNOSIS OF ULCERATIVE TUBERCULOUS COLITIS

By LAWRASON BROWN, M.D.

AND

HOMER L. SAMPSON

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The clinical diagnosis of ulcerative tuberculous colitis, particularly in its early stages, is seldom made positively, clinically. In view of the fact that operative procedure may definitely cure this complication of pulmonary tuberculosis, if taken early enough, means for making a definite diagnosis are very desirable. Tubercle bacilli in the stools are of little value; in fact, there are no laboratory tests upon which much dependence can be placed.

The symptoms at the onset are often so slight that they apparently occur at times in normal individuals who have slight gastro-intestinal disturbances. Diarrhea, at times of very slight moment, and transitory, may be an early symptom, though marked constipation can be present.

Stierlin of Basel reported six cases in 1911, operated on by Willms, in which Stierlin made a diagnosis by means of *x*-ray. Pirie, who studied the cecum at Archibald's suggestion, says that in 12 of Archibald's 27 cases he was unable to visualize it.

The technic employed in the 110 cases—the basis of this paper—was to have the patient abstain from taking any laxative the day before the examination. At an appointed hour the next morning he was given a barium suspension on an empty stomach (formula: 1 tablespoonful each of cocoa, sugar and flour, 4 ounces of barium, and milk to make 16 ounces. Six hours after taking the meal the patient is examined fluoroscopically and roentgenographically. If

no barium has reached the cecum, or if the cecum is not well filled and there is still barium in the ileum, an examination should be made every half-hour for the next hour or two. Plates are taken. A second examination is made at the end of twenty-four hours. A day or two later, the patient, having taken an ounce of castor oil eighteen hours before, is given a barium enema at low gravity pressure, from 10 to 12 inches, and the injection is observed fluoroscopically. The enema is stopped as soon as it fills the cecum or passes through the ileocecal valve.

Normally the stomach empties itself in three to six hours. The head of the barium meal reaches the ileocecal valve in one to three hours. The ileum empties itself in five to nine hours. The cecum is seen in from two to four hours after ingestion; six hours after the meal has been taken the head of the column is seen at the hepatic flexure or splenic flexure. Complete evacuation takes place in from thirty-six to forty-eight hours. The cecum remains well or partially filled from the fourth to the thirty-sixth hour.

In tuberculous ulcerative colitis the head of the column is often seen in the sigmoid and rectum in six hours, while at the same time there may be a small retention in the stomach. At the end of twenty-four hours there may be a small amount of barium in the sigmoid or rectum, or the bowel may be comparatively empty. The second and probably the more important manifestation is the spastic appearance of that portion of the bowel later proved to be involved. Usually in the cecum or cecocolon the smooth haustral sacculations are absent and the bowel has a distinctly irregular and ragged appearance. It is usually only partly filled.

Under the fluoroscope the barium is seen to pass quickly through the cecum even when vis a tergo could apparently be excluded. The fluoroscopic studies of the barium enema reveal what may be interpreted as a spasm of the suspected portion, which rarely fills well, and if it does, may almost instantly empty itself completely of barium.

In all 110 cases were studied; 3 were negative and 6 only suspected of pulmonary tuberculosis, 11 cases were incipient, 68 moderately advanced, and 22 far advanced pulmonary tuberculosis. Among the negative and suspected or doubtful cases of pulmonary tuberculosis

there was no roentgenologic evidence of tuberculous colitis, though some presented symptoms similar to those who were found to be positive.

Three of the 11 incipient cases were positive; 1 was proved at operation, 1 died of pulmonary and intestinal tuberculosis(?), 1 is alive and has not been operated upon.

Of 68 moderately advanced cases, 44 were negative, 15 were doubtful, and 9 positive. Of the 9, 4 were proved at operation.

Of the 22 far advanced pulmonary cases, 5 were doubtful, 17 were positive. Of these 5 doubtful cases 3 were not operated upon, and 2 are dead. Of the 17, 9 were verified at operation, 3 died, and 5 were not operated on. The operative findings tallied very closely with the diagnosis as to site and extent, though some were not extensive.

Through the kindness of Drs. Robert M. Brown, R. C. Paterson, S. F. Blanchet and C. C. Trembley, we have been enabled to study roentgenographically some of their cases. It is interesting to note that in the second set of similar cases the results were identical with those mentioned above. It should be noted that absence of these findings does not exclude tuberculous ulcerative colitis, and further, that a few doubtful cases occurred which further study might have revealed to be positive.

Conclusions. 1. Tuberculous colitis can be diagnosed clinically with a considerable degree of certainty when the disease is far advanced.

2. On the other hand, in the early or latent stages, when remedial measures may prove of avail, the clinical picture may be of little aid in diagnosis.

3. In all stages, certain shadows cast by the barium meal at the end of six, eighteen and twenty-four hours determine definitely the presence of colonic ulcerations, but the absence of such shadows does not absolutely exclude colonic ulcerations.

4. The roentgenologic picture shows hypermotility and spasm, or filling defects.

5. The presence of such a picture in a patient with pulmonary tuberculosis should lead to a definite diagnosis of colonic tuberculosis.

6. Tuberculous colitis occurs far more frequently than hitherto supposed, and must be excluded in all advanced cases and in any early case with any abdominal symptoms, before submitting the case to radical treatment.

7. No examination of a patient with pulmonary tuberculosis can be considered today complete without a roentgenologic study of the intestine.

IMMINENT PSYCHOLOGY—A PROPHECY AND A PLEA

By JOSEPH COLLINS, M.D.
NEW YORK

After we have had an encounter that tests our capacity and our endurance we should submit ourselves to examination that we may know our actual and potential strength. After a merchant or a banker has had unusual and testing demands made upon his stock or his capital he deems it not only prudent to take an inventory but imperative.

The medical profession of this country has been called upon the past two years to give an account of its competency that tested it to a degree never imagined or anticipated. That it was not found wanting, spiritually or materially, is gratifying; that it was found inadequate in some respects is regrettable. It should be our desire and our duty to surmount the conditions upon which such inadequacy depended. It is meet that we should profit by our experience. We read and we hear it said by surgeons and physicians that aside from certain standardizations we have not learned much from the war, meaning that no new principles in pathology, bacteriology or chemistry have been established or elucidated. But if the war has shown us that our training as physicians is imperfect, and, in some ways, inadequate, we have learned that which may profit mankind far more than the discovery of a new antiseptic or a new treatment of wounds.

I confine my remarks to the department of medicine, with which I am identified, neurology, which, of course, I use to include disorder of the mind, emotions, personality, soul, that which is man's god-like possession, call it what you will.

Statement of Fact. The medical profession was unprepared to make adequately, properly and expeditiously, the examinations

which would eliminate from the volunteer and draft men actual and potential disorder of the nervous system.

It was incompetent, in a measure, to examine, interpret and treat disorder of the nervous system flowing from war and its entailment.

It is not prepared now to do the work of reconstruction as well as the medical profession of some other countries.

The explanation of this dereliction is that (1) the branch of medicine known as neurology has never been properly or adequately taught medical students in this country; (2) the branch of physiology known as psychology has been treated by medical pedagogues and practitioners with scorn; (3) alleged and admitted psychiatrists have not considered it essential to be physicians, diagnosticians, interpretists and therapists first and psychiatrists second.

The war revealed the fact that, next to injury and general medical diseases, disorder of the mind and nervous system was the most incapacitating disease of soldiers. It convinced the medical personnel of the army that training in neurology and psychiatry was essential if the average medical corps man was to do his work properly. The experience of neurological and psychological examiners at officers' training camps and at cantonments showed that large numbers of enlisted and volunteer men, officers and soldiers were of such intelligence that they were not fitted for officers or soldiers and that many actual and potential nervous and mental diseases were to be detected by careful examination. Out of 1,700,000 men examined by psychological tests, approximately 47,000 were found to be the mental age of ten years. From 3 to 5 per cent. of the men in officers' training camps were found to be afflicted with some form of nervous or mental disease that either incapacitated them or would incapacitate them under stress.

The importance of neurology in medical practice in the war is convincingly illustrated by the experience of France and England. For three generations France has had neurological schools through which large numbers of its physicians passed and in which they not only learned the fundamental principles of neurology but became familiar with cardinal methods of examination. As the result of this the medical profession in France was so enlightened that they were able to provide two important regulations in the matter of

shell shock. (1) That victims of that so-called neurosis were not pensionable, and (2) that its occurrence was not an adequate cause for discharge from military service. This enlightenment of the medical profession of France saved many thousands of soldiers and millions of francs for that country. On the other hand, neurology in England has never had extensive recognition by the general practitioner. As the result, she has some 25,000 men who are pensioned, invalid soldiers, most of whom were recoverable had they been properly diagnosed and treated.

THE PROPHECY. We are now on the threshold of an era in which psychology is going to be applied to the problems of mundane life: work, occupation, recreation; the spiritual, physical, social, financial, hygienic betterment of mankind, including ourselves.

Within a generation admission to high schools, colleges and universities will be obtained, in great measure, by passing a psychological examination. It will be obtained by determination of the candidate's intelligence and his emotional reactions and not by determination of how much Latin or Greek or algebra or history he has been able to memorize.

Within the same period anyone seeking a position of responsibility, or that requires for its satisfactory performance intelligence, will be required to pass a psychological examination, and upon that examination will depend largely the fate of the individual.

The choice of profession, occupation or career will be determined largely by psychological examination of the individual. In this way the misfits will be prevented. Men and women adapted for the church will not go into medicine; those adapted for the stage will not go into finance; potential statesmen will not strive to be scientists.

Fitness for taking on work that requires for its successful accomplishment attention, energy, vision, imagination, any constructive mental quality will be determined by psychological and physical examination. Civil service examinations will no longer consist of geography, history, algebra and similar subjects; entrance to the diplomatic service will not depend upon knowledge obtained from books; promotion or advancement in any intellectual field will not be dependent upon feats of memory. They will be determined by psychological examination of the individual seeking position and preferment.

The next great move that pedagogy will make will be in the field of psychology. There will be a radical change in the present method of grading schools. The grading of pupils will soon be done by determining the constitution of their mind, its potentialities, the trend and capacity of its contents. Children who have aptitudes, special qualities of mind or emotion will be grouped, while others lacking these but possessed of equally meritorious mental and emotional qualities of a different kind will be classed in another group, and they will be subject to different kinds of instruction.

Vast sums of money will be saved taxpayers and great numbers of individuals will be saved lives of incompetency and ignominy by the utilization of the facts that have today been established by psychology. Potential psychoneurotics will be recognized before deforming and incapacitating nervous and mental symptoms appear; the feeble- and tender-minded will be detected at a time when developmental measures may be applied, with hope of success; and those from which are recruited cranks and criminals, prostitutes and wastrels, drunkards and hoboes, will be recognized to be the legitimate care of the State and of the individual, whose combined effort must be to assist them to approximate normality before they have, by accident or design, offended law or convention.

Many chronic diseases and much semi-invalidism which cannot be specifically designated depend upon disorder of internal secretions, that is upon disturbed functions of glands controlled and regulated by the nervous system and which develop and operate in connection with the emotions.

Health, resistance to disease, mental and emotional endowment, the things that make life worth living, are as intimately bound up with the origin and development of the sympathetic nervous system, and this in turn with instincts and emotions, as man is bound up with original sin. The physician who seeks to interpret them and prevent them thrusts a great handicap upon himself by ignoring these facts, and he who devotes his life to ameliorating or attempting to cure disease obstacles himself tremendously by not hearkening to the revelations of the science of psychology.

Medicine is about to be quickened, revived and enriched by doing teamwork with the science of psychology. Though the prevention

of disease is and must always be the goal for which its votaries strive the amelioration and cure of disease will continue to engross the vast majority of them. Psychology will, however, be utilizable in both fields. Already the man of affairs, the man of big business, is utilizing it by means of a new type of efficiency expert, the social and psychological engineer.

Preventive medicine must concern itself with the individual as well as with the germ. Resistance to disease may be partly a question of chemistry, but it is largely a question of emotions and psychophysical elaborations, whose potency may be determined, and their existence influenced, by the physician versed in psychology.

To speak of the effect of mind upon matter before this audience, or to dwell upon the influence of mind upon disease in a country in which supernaturalism thrives so luxuriously as it does in this country, would be absurd. We physicians are about to be compelled to use forces scientifically which innumerable "ists" have used, and are using with such success, empirically.

The Plea. The members of this Association are the medical teachers of the country or the material from which the dominating medical teachers are recruited. It is to them that the rank and file of the profession, and the laity conscious of hygienic and social awareness, look for inspiration, guidance, initiative and accomplishment. They are the tune that makes the Esculapian music.

I appeal to you, therefore, to treat neurology as a legitimate child, worthy not only of parental affection and understanding, but entailing the obligation of development and maintenance, of fullest and most intimate admission to the family medical circle.

It would be no more absurd to maintain that a physician could be competent who was ignorant of physiology than it would to claim that one could be a competent neurologist who had not a comprehension of psychology. Psychology should be hailed with the warmth that chemistry was a generation ago. It gives promise of results equal to or surpassing those obtained by the physiological chemist.

Psychology should be taught medical students, or a comprehensive familiarity with its fundamental principles should be demanded of those who knock at the portals of medicine as a career. Psychiatry

should be taught in medical schools as pathological physiology and as a division of internal medicine—one of the most important divisions. The psychiatrist should be a thoroughly trained physician who has a bias toward, or flair for psychology. The training in medicine should give him perspective; the training in psychology, penetration; and both should give judgment of fundamentals, which in physicians is often spoken of as insight, perspicacity, awareness—qualities essential to the real physician.

The successful physician of the future must make a biological study of human nature and instinct if he would fulfil his privileges and discharge his duties. In no other way can he compete with the empiricists, supernaturalists and neoplatonists who have reaped such harvest in this country at the expense of the victims of incapacitating disorder of one or more of the bodily functions masquerading as disease of the nervous system.

To give such training there must be hospitals and laboratories as well as teachers. The unstudied, uninterpreted material in general hospitals, and the casual, transitory material of the dispensary is neither appropriate nor adequate. We must have hospitals for the study and interpretation of nervous diseases in connection with every school in which medicine is properly taught.

The career of the Neurological Institute of New York is an earnest of the need of such hospitals, and the service it rendered this country in giving rapid, intensive training to upward of three hundred physicians which would endow them with a measure of the capacity necessary to handle the neuropsychiatric problems presented by the war is the reward of its founders.

The present proud position of the science of medicine is attributable to one factor—the laboratory. The elimination of disease by preventive measures has, in a measure, been accomplished by it and will continue to be accomplished by it. No less than twenty-five diseases are diagnosticated with certainty by laboratory methods, and the recognition of at least a score of others is assisted and facilitated by it.

Laboratory methods receive greater emphasis in medical education than any others. The psychological laboratory only is neglected and yet the technicians of the psychological laboratory made one

of the important contributions of medicine in the war by the formulation of methods of mental and emotional measurement which permitted elimination of men unfit to contribute to military success and facilitated proper placement of officers and soldiers.

We cannot hope, nor would it be desirable, to make physicians into psychological laboratory technicians. The latter must be the assistant to the physician, just as the bacteriologist, the chemist and the photographer is. He must be the expert coöperating with the physician. They must do teamwork. They cannot do it if the physician balks and, instead of pulling, expends his strength in scorning the psychologist. The physician must be the judge of the psychologist's work; he must test it, and he must know how to utilize it for the benefit of the sick.

It is not sufficient that the leaders of medical thought and the makers of the pace of medical efficiency shall say that they are ready and willing that the psychologist shall show them what he can do. They must do with the principles and formulations that he furnishes that which they did with those discovered and formulated by Pasteur.

Neurology and psychiatry must be properly taught in this country if American medicine is to get and maintain the place which it deserves. To accomplish this three things are necessary: (1) Teachers; (2) hospitals; (3) the sympathetic atmosphere. The last is vital. I appeal to this organization to furnish it.

DISCUSSION

Dr. Adolf Meyer said the great difficulty about psychology so warmly appreciated by Dr. Collins is the fact that those who wield the power in the distribution of funds for investigation still seem to suffer of mind-shyness. Today we might well eliminate the charge of vagueness for this field. We deal with perfectly concrete facts, and I hope that neuro-psychiatry will soon begin to receive, as a token of confidence and pragmatic interest, at least half-way adequate support from our national scientific foundations.

THE SIGNIFICANCE OF RICKETTSIA IN RELATION TO DISEASE

By RICHARD P. STRONG, M.D.
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In 1916 Rocha-Lima called attention to the presence of very minute bodies which were found in lice which had fed upon patients suffering with typhus fever. These bodies were present not only in the contents of the alimentary canal, but especially in the epithelial cells of the alimentary tract of these insects. He regarded them as very minute microörganisms. They were eliptical, oval, often found in pairs and bipolar in appearance. The smallest forms measured from about 0.3 to 0.4 micron and the larger ones, sometimes biscuit-shaped, from 0.3 to 0.9 micron. They were best demonstrated by staining in Giemsa's solution. These organisms were not at first found in lice which had not fed upon cases of typhus fever. The lice were said to become parasitized only after ingesting infected blood. Rocha-Lima pointed out that while these bodies slightly resembled bacteria in their morphology, they were in other respects more like the Chlamydozoa strongyloplasmata. He therefore proposed for them the name of Rickettsia prowazeki (n. g., n. sp.) evidently choosing this name in memory of Ricketts and Prowazek, both of whom succumbed to typhus fever which they contracted while pursuing their independent investigations upon this disease. Subsequently, organisms having a similar appearance were found by other observers and also by Rocha-Lima in lice which had fed upon healthy individuals or on those suffering with various other diseases. For this second form Rocha-Lima proposed the name of Rickettsia pediculi. He believes that Rickettsia pediculi differs from Rickettsia prowazeki in that the former is found normally only in the lumen of the alimentary canal of the

louse, and does not multiply in the cells of the insects' alimentary tract, or only does so exceptionally.

It is of importance in considering the study of the rickettsia to recall that the terms chlamydozoa (Prowazek[1]) and strongyloplasmata (Lipschutz[2]) were proposed to include a group of very minute pathogenic organisms or viruses which exhibited certain common properties, while exercising specific peculiarities in each case. These viruses are believed during at least one stage of their development (that of the "elementary corpuscles") to pass through bacterial filters without losing their virulence. Within the cells of the host the elementary corpuscles are believed to grow into larger "initial bodies." The chief characteristics of the chlamydozoa[3] were said to be: (1) their minute size, smaller than any bacteria hitherto known, enabling them to pass the ordinary bacterial filters during one stage of their development; (2) that they develop within cells, in the cystoplasm or nucleus, and produce characteristic reaction products and enclosures of the cell; (3) that they pass through a series of developmental stages and are specially characterized by their mode of division, which is not a simple process of splitting as in bacteria, but is effected with formation of a dumbbell-shaped figure as in the division of a centriole. Two dots are seen connected by a fine line like a centrodesmose, which becomes drawn out until it snaps across the middle, and its two halves are then retracted into the body. In appearance the chlamydozoa seem to consist primarily of merely a grain of chromatin without cytoplasm and without a membrane of any kind. Hence they appear to represent the simplest form of living body. The chlamydozoa have not yet been successfully cultivated, but infections can be produced with pure colloid-filtrates free from bacteria, but containing the minute bodies themselves. They are characteristically parasites of epiblastic cells and tissues. The viruses of trachoma, vaccinia, scarlet fever, hydrophobia, molluscum-contagiosum, and more recently of typhus fever, have been referred to the chlamydozoa.

[1] Archiv. f. Protistenkunde, 1907, x, 336.
[2] Handbuch der Pathogenen Protozoen, Leipzig, 1911, Prowazek and others.
[3] Minchen: Introduction to the Study of the Protozoa, London, 1917, p. 472.

Previous to Rocha-Lima's observations, several investigators had published articles describing microörganisms observed in lice which had fed upon typhus fever patients, and Ricketts described a somewhat similar organism in connection with Rocky Mountain fever. Therefore, while it is advisable to consider these investigations in chronological order in connection with the discussion of this subject, lack of time will not permit of this being done here today. (These will be given in a table when the article is published in the Proceedings of the Association.)

Our own studies regarding the occurrence of Rickettsia bodies in lice which have fed upon healthy persons have confirmed those of a number of observers already referred to. Lice collected from healthy men in different parts of France where neither typhus fever nor trench fever were present, were often found to contain rickettsia in their dejecta; from 20 to 40 per cent. of such lice examined, collected in different groups, revealing these bodies. In some of these normal lice, microscopical examination of the excreta or material from the alimentary tract showed them to be severely infected with rickettsia bodies. Others were only moderately or very slightly infected, while in the remaining no definite rickettsia were observed. Obviously from a microscopical examination, it is sometimes extremely difficult to say whether these bodies are not present in small numbers in the lice. (Plate I, Figs. 1 and 2, demonstrate the rickettsia bodies in the excrement of *normal* lice.[1]) The lice are referred to as normal because they produced no disease either in their original host from which they were collected or when they were placed upon or fed upon other healthy individuals.

A critical examination of the literature regarding the relation of rickettsia to disease reveals the fact that these bodies have been found in lice which have fed upon cases of typhus fever, wolhynian fever, trench fever, war nephritis, malaria, bronchitis, inflammation of the bladder and inguinal hernia, as well as in a large number of lice collected in different parts of the world which have fed only on healthy people in whom they produced no disease. It is true that

[1] These photomicrographs were kindly made at the Pasteur Institute by Dr. P. Jeantet, who is in charge of the photomicrographic work of this Institute. I wish to express my thanks both to Dr. Roux, the director of the Pasteur Institute, and to Dr. Jeantet, for this courtesy.

in lice, Rocha-Lima suggests that Rickettsia prowazeki, which is regarded by him as the probable cause of typhus fever, differs from Rickettsia pediculi, which is found in lice not infected with the virus of typhus, in that the latter does not occur normally in the epithelium of the alimentary canal of the louse. However, Topfer, Brumpt and others have found rickettsia in the intestinal epithelial cells of lice fed upon healthy individuals as well as in those fed upon wolhynian fever cases and cases of war nephritis. Rickettsia have also been found in ticks that have fed upon cases of Rocky Mountain spotted fever. They have in addition been observed in the blood of man in a number of diseases, for example, in typhus fever, in Rocky Mountain spotted fever, in wolhynian fever, and trench fever. Rocha-Lima also believes that he has seen in the blood of healthy persons similar bodies to those observed in the blood of wolhynian fever by other investigators, and described by them under the name of rickettsia.

Further, when we come to consider the etiological significance of rickettsia in human disease, it is apparent from the evidence already presented in this article that not one of the three classical postulates regarded necessary for the proof of the etiological factor of an infectious disease is fulfilled by the rickettsia. (1) They have not been found in every case of the disease they have been said to be the cause of; moreover they have been found in connection with other diseases than the one it is maintained they give rise to. (2) They have not been isolated and grown in pure culture. (3) The disease which they are said to be the cause of has not been produced by the inoculation of such culture.

It is very possible that the rickettsia bodies are microörganisms, but as they have been found in lice from patients with so many different diseases, as well as in lice from healthy individuals, obviously no specificity for them can be justly claimed at the present time. It is true that Rocha-Lima, Topfer, and Olitsky, Denzer and Husk claim to have produced typhus infection in animals by the inoculation of the contents of the alimentary tract of infected lice. In this connection Rocha-Lima claimed that the disease developed in the inoculated animal because the rickettsia were present in the lice used for the injections, while on the other hand, Olitsky, Denzer

and Husk claim the disease developed because the Plotz bacillus was present in the lice used in the inoculation of the animals. Obviously we can draw no definite conclusions from these experiments save that the infecting agent, visible or invisible, was present in the lice. Nothing can be said from them regarding the definite nature of the infecting agent. Seargent, Foley, Vialette, and Brumpt all pointed out that the rickettsia might merely accompany the infectious agent.

Some further light has recently been thrown upon the significance of the rickettsia by observations and experiments which we have made in connection with trench fever. In relation to the etiology of trench fever, as has been the case in the history of most infectious diseases, a number of widely differing microörganisms have previously been described as its cause, but none of these claims have been substantiated, and although very extensive studies have been made by a large number of observers, it is still a question whether the organism causing trench fever has yet been definitely seen in man either with the microscope or the ultra microscope. Our experiments carried on in relation to the etiology of trench fever have since shown that this disease is caused by a filterable virus which bears some resemblance in its behavior to the filterable virus of hog cholera.[1] Our work regarding the filterable qualities of the virus of trench fever has recently been confirmed by Major-General Sir John Rose Bradford, Captain E. F. Bashford, and Captain J. A. Wilson.[2] The organism causing trench fever, being so minute, is obviously separated only with great difficulty from the surrounding structures in the media in which it occurs naturally. Thus, while we have demonstrated that the virus of trench fever is present free in the plasma of the blood of trench fever cases, in the febrile stages of the disease, it is frequently very difficult to separate it from the blood corpuscles themselves by repeated washings of these with saline solution.[3] Also in the alimentary canal of the louse fed upon trench fever cases and in infected louse excrement, the virus on account of its minute size is closely intermingled with other cellular structures present.

[1] Trench Fever; Report of Commission of American Red Cross Research Committee, Oxford, 1918.

[2] British Med. Jour., 1919, 127.

[3] Loc. cit.: Trench Fever Report, p. 27.

We have also emphasized that in different examinations of lice fed only upon healthy individuals, the rickettsia have been demonstrated in from 20 to 74 per cent. of them. Knowing these facts, let us suppose that lice already containing such rickettsia in variable number had been fed upon trench fever cases and had become infected with the virus of trench fever, and such lice (containing that rickettsia which may in the meantime have multiplied or increased in number) were then placed upon healthy human beings whom they subsequently infected with trench fever, obviously then erroneous conclusions might be drawn that the rickettsia were themselves the etiological factor of trench fever. It is evident that great difficulty would be experienced in a separation of the virus of trench fever from such bodies under the circumstances described above. Probably only by successful filtration experiments such as we have performed with lice excrement in connection with trench fever, could the separation be accomplished.

It of course may be argued that rickettsia have a filterable stage as have other so-called chlamydozoa, and this idea receives some support from the fact that the virus of trench fever is under some circumstances filterable with difficulty, and attempts to infect human beings with the filtrates of infected material are often unsuccessful. Thus in ten filtration experiments performed with infected blood and urine from trench fever cases and infected louse excrement, only three gave undoubted positive results. The temperature charts of two cases of trench fever experimentally produced by the injection of the filtered trench fever virus are illustrated in plates II and III.

Bradford, Bashford, and Wilson[1] have since reported upon the cultivation of the trench fever virus from filtrates which have previously passed through porcelain filters, and have also shown by human experiments that such filtrates contain the infectious agent.

It is conceivable that the rickettsia, whether they possess a filterable stage or not, may be parasites of lice and not pathogenic for man, and Brumpt has suggested that the finding of them in human blood may simply be an indication that the individual has been previously infected with lice. On the other hand, there is the

[1] Loc. cit.

possibility that the bodies sometimes described as rickettsia may constitute products of degenerated cells, for example, basophilic granules, which are more numerous in the blood in certain febrile diseases, in which case they would also increase in number in the lice fed upon such cases, and might then merely accompany the very minute or invisible etiological factor of the disease.

In connection with the significance of rickettsia as an etiological factor in typhus, trench fever, and other diseases, it may be of interest to recall that in 1903 an organism described by Parker, Beyer, and Pothier as Myxococcidium stegomyiæ was found in infected stegomyia mosquitoes, and was for a time supposed by these investigators to be the parasite causing yellow fever. Later this organism was found to be a species of yeast, and to occur not only in mosquitoes infected with the virus of yellow fever, but also in those not infected with such virus, and the virus of yellow fever was shown to be filterable and ultramicroscopic. Noguchi's[1] recent experiments, however, suggest that the organism of yellow fever may be a spirochete which is filterable at least at one stage of its life history.

From a review of the evidence presented in this paper regarding rickettsia, it appears obvious that, until more definite results are obtained from further experimental work, we are not justified in concluding that the rickettsia have a definite specific etiological significance in relation to human disease.

[1] Jour. Am. Med. Assn., 1919, lxxii, 187.

CHRONIC TRENCH FEVER

By R. D. RUDOLF, M.D.
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Trench fever has for some time now been a recognized disease in the army. So many cases, indeed, are diagnosed as such that the term has almost displaced the old military one of "P. U. O." (pyrexia of unknown origin). Probably in most cases this is a correct diagnosis, as trench fever is undoubtedly the most common infection at the various fronts.

McNee[1] originally described two forms of the disease: A "short" and a "long" one, and the British Trench Fever Commission[2] three forms. The American Trench Fever Commission very properly called attention to the difficulty of making all classes fit into these or any definite classes. The intermittent "spiked" type of the disease (McNee's "long type") is very characteristic and can scarcely be taken for anything else, but many of the other forms cannot be diagnosed clinically from the mere inspection of the temperature charts.

A Pagenstecker[3] described four irregular types, as follows:

1. The majority of cases. The febrile bouts occur at intervals of two to five days and extend over several weeks; the initial rise of 102° or higher is almost always followed by a critical fall on the next day, and then an apyrexial period, with some slight irregularities supervenes, until the next bout of fever. The height the temperature reaches is always less than the previous one.

2. Resembles the first form, except that the temperature takes some days to fall by lysis.

[1] British Medical Journal, 1916, i, 225.
[2] Ibid., January 19, 1918, p. 91.
[3] Deutsch. med. Wchnschr., Berlin and Leipzig, 1918, xliv, 235-236.

3. The temperature suddenly runs up to 104° or more at a time when the individual feels perfectly well; next day there is a fall of temperature, with profuse sweating. In the majority of these cases the blood is examined for the malarial organism, with negative results.

4. With continued fever, always below 100.5°, lasting for weeks or months, and with marked subjective symptoms of trench fever.

It is this fourth chronic type that one sees so much of in convalescent camps and among men of low categories, and it is the one that will be the most important to recognize after the war. On account of its resemblance to chronic malaria the writer ventured some months ago to refer to it as trench fever cachexia.[1] For months and even years the patients remain in a low state of health, with slight occasional or constant elevation in temperature, often with an enlarged spleen and some anemia, and nearly always with pains in various parts of the body.

The American Trench Fever Commission wrote as follows: "Failure to recognize the persistence of the infection has led to a disregard of slight fever, such as 99° to 99.5°. In most hospitals the temperature is neither taken every four hours nor frequently enough to detect short relapses. The pulse-rate, although taken, is often not recorded. No doubt every medical officer who has had much experience at the base hospitals has been struck by the number of patients who give a history of a previous illness, which was probably trench fever, and who at the time of examination showed tachycardia, slight pyrexia and some other slight symptoms of trench fever, all these probably pointing to a continuance of the infection."

We do not yet know how long these cachectic cases may last. Colonel A. B. Soltau[2] speaks of having followed them for four years. He refers to them as the "smouldering" type of the disease, and says that after a man has had an acute attack "the infection has smouldered on, causing debility and accompanied by an irregular temperature, occasionally running up to 100° at night, but always down in the morning. It is this type of case that is so commonly diag-

[1] Lancet, December 14, 1919, p. 809.
[2] Ibid., December 28, 1918, p. 893.

nosed as 'myalgia,' whereas true myalgia is exceedingly uncommon. Only careful examination of the temperature curve and the type of the pain will enable a correct diagnosis to be arrived at."

At one of our special hospitals in England devoted to the care of "myalgic" cases I had the temperatures of all the patients taken very carefully, and found that about 15 per cent. of these were slightly elevated at some time in the twenty-four hours, and examination of the patients showed that probably most of them were examples of trench fever cachexia. At another hospital for "D. A. H." cases quite as large a percentage of the patients showed some fever. It may be remembered that the report of the Military Heart Hospital at Hampstead showed that many of their "D. A. H." cases had slight fever. The probabilities are now that many of these cases were examples of still present trench fever infection.

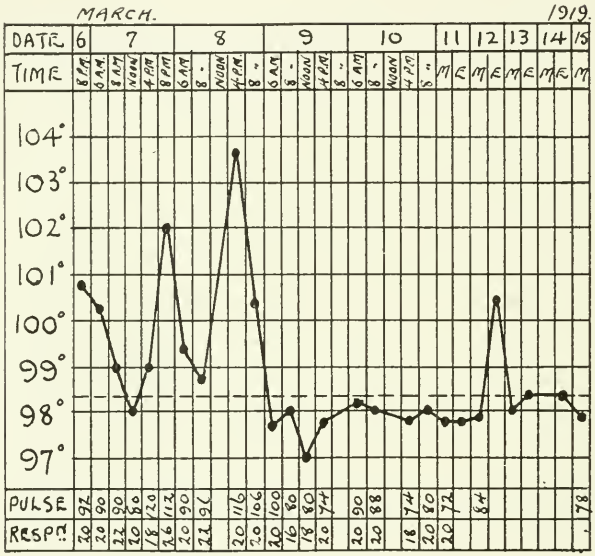
If the temperatures of soldiers at convalescent hospitals and in low category work who are complaining of debility, pains in various parts of the body (especially the shins) and of the "effort syndrome" be taken, it is surprising how often slight degrees of fever will be detected. Many of these men have been away from the front for over a year, but have never felt well, and their "medical history sheets" usually show that they have been admitted to hospital again and again since reaching England. Many have been invalided out of the army under such diagnoses as "debility," "anemia," "D. A. H." and "myalgia." Some of them would return to homes where the body louse is a regular inhabitant, and no doubt the disease will thus be spread among the civil population. Major Byam, of the Hampstead Trench Fever Commission, found that lice could be infected from chronic cases of as long as seventy-nine days' standing. Already cases are occurring in our camps in England among men who have never been abroad but who have been quartered with returned soldiers. Case I is an example of this. It is that of an officer who had served in a rest camp among soldiers who had returned from France. The officer himself had not been at any front and had recently come from Canada. He had on several occasions found lice on his clothes.

Types of Chronic Trench Fever. Chronic trench fever may present several different forms of temperature curves, as follows:

1. Continued slight fever.

2. Occasional bouts of fever.

3. The afebrile type: (*a*) Showing symptoms of trench fever but with no alteration in the temperature curve; (*b*) showing a swinging temperature curve.

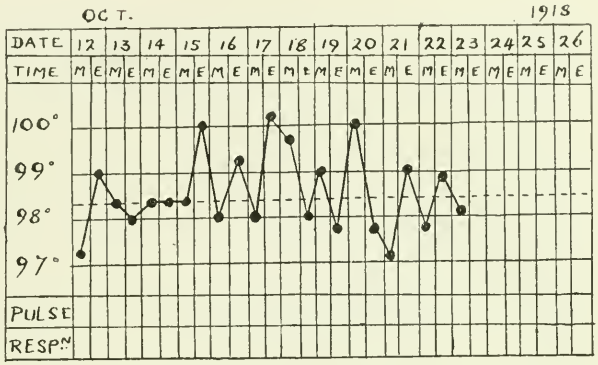


Case 1.—Captain H. Suffering from fever and pains in head and shins. Had never been in France or at any front, but on several occasions had been lousy. (See Case 7.)

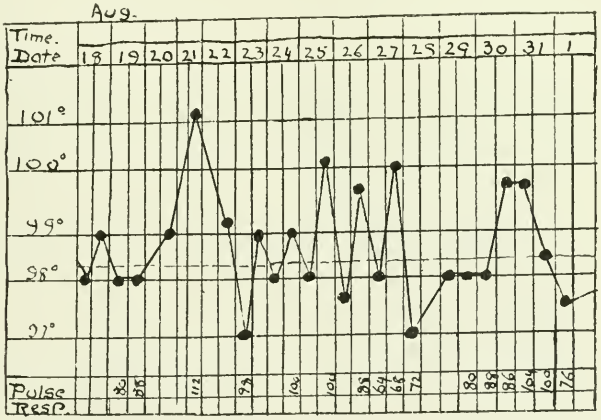
1. This common type shows an almost continual elevation of temperature. The whole curve is set a degree or two too high. Cases 2, 3, 4 and 5 illustrate this type and every clinician can duplicate such charts indefinitely. Patients showing a little fever are studied for such conditions as tuberculosis, various sources of sepsis or toxemia, etc., but many show no such cause for their fever, and when the special symptoms of trench fever are looked for frequently are found to be examples of this infection.

2. Occasional fever with periods of normal temperature. Some of the long-continued "spiked" cases might be put into this class, although they may more properly be considered as acute relapses of the disease. Case 6 is an example of this. But there are chronic

cases which show the same rhythmical periodicity, although the rise on each occasion is very slight. Case 7 is an illustration of this.



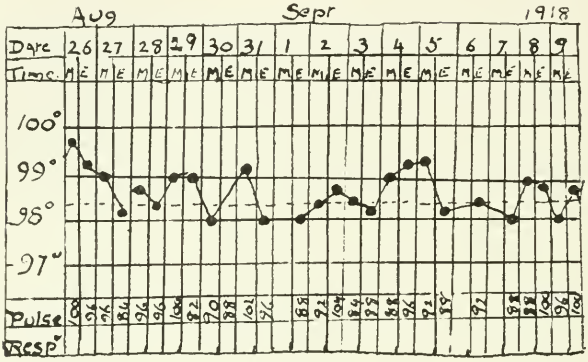
Case 2.—Private A. This man was invalided from France a year ago as a case of trench fever. He had been poorly for several weeks before leaving that country. Has been feeling out of sorts ever since, with aching shins and shortness of breath on exertion. His medical history sheet shows that he has been in various hospitals and has always had slight fever. The chart illustrates the slight chronic type of fever.



Case 3.—Private H. Was invalided from France on May 23 (*i. e.*, over three months ago), and had been feeling ill for several days before he "went sick." Since reaching England has been poorly, with headache and aching shins and back, all the pains worse at night. No local condition found to account for the pains. Temperature has been running as in chart ever since his arrival in England, over three months ago.

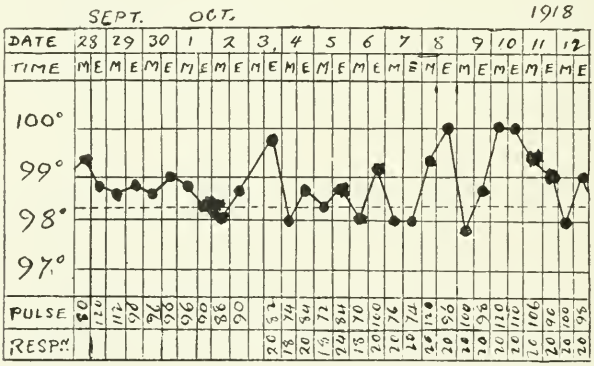
The chart is from the same patient as Case 1, but months after the acute condition was over.

3. This class might be called the afebrile type of trench fever and there are two distinct subdivisions of it: (*a*) In one there is no



Case 4.—This is the chart of the same patient as Case 6, only taken four months later. The case has now become one of the cachectic type.

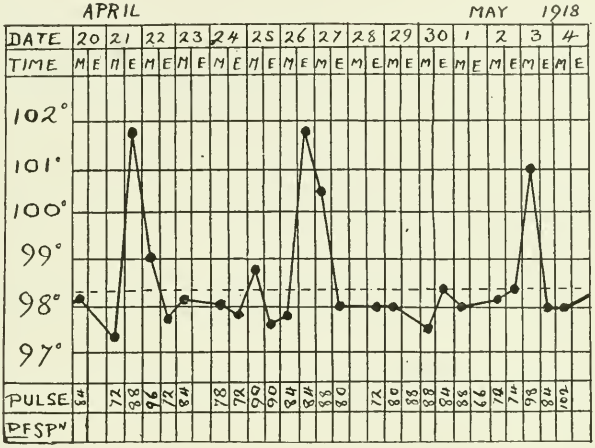
disturbance of temperature, but the patient has had the acute infection and still is suffering from the pains and other symptoms. Such a case may at any time show an exacerbation. Case 8 is an



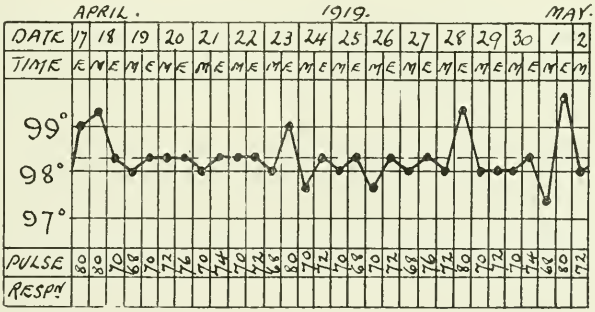
Case 5.—Private S. Took ill in France on July 28 (two months ago) and was invalided to England as "trench fever." Since then until the time that this chart was made he had felt poorly, with aching shins. Temperature was up on the average about 2°, with no definite intermissions. No local cause for the pain in the tibiæ could be found.

example of this. The man had recently had an acute attack, was now afebrile but full of pains, and soon after this chart ends was

once more febrile due to a relapse. (*b*) Several writers have called attention to a type of trench fever in which the temperature curve



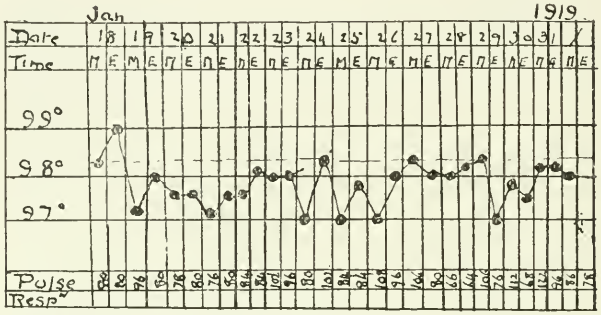
Case 6.—Private M. was invalided from France the day before this chart commences, but had been "sick" for some weeks with recurring attacks of fever. The chart shows the typical "spiked type" of trench fever. It is the "long type" of McNee. (See Case 4.)



Case 7.—Captain H. This chart is from the same patient as Case 1, only illustrates his condition several months later. It shows slight rhythmical rises in temperature, and the patient can always tell from a headache and slackness, when these are going to occur. (See Case 1.)

seldom rises above the normal line, but is peculiar in that it swings several degrees between morning and night, being perhaps 95° in the morning and 98° or 99° at night. Case 9 shows this form of curve.

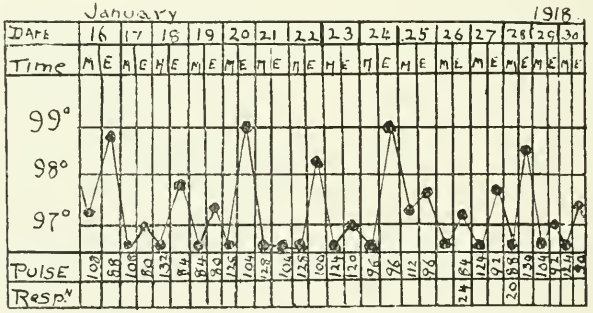
Symptoms. Apart from the pyrexia the most characteristic symptoms of trench fever are pains in various parts of the body, palpitation and other signs of the "effort syndrome," general



Case 8.—Private L. This man has recently had an acute attack of trench fever. At the time that this chart was made he was free from fever, but full of pains and very limp. A day or two later he had a severe relapse.

malaise and debility and certain special symptoms as described below:

1. *Pains.* Next to the fever the pains are the most characteristic symptoms of this disease. At the onset headache is practically



Case 9.—Private A. This patient was invalided from France several months ago with trench fever and has been poorly ever since, with anemia and aching shins. His chart shows the type of chronic disease where the temperature swings greatly, but is seldom above the normal.

constant and is often severe and is even suggestive of meningitis. It may be generalized or occipital. It tends to recur, with each relapse, but not to the same degree as at first. The head is often

peculiarly tender, especially in the supraorbital region, and the eyes ache.

Lumbar pain comes next in frequency and resembles lumbago and there may be much tenderness in that region.

Pains may occur anywhere in the extremities, but are so common in the shins that the disease has been called "shin fever" or "gaiter fever." In my experience this is the commonest form of pain, and it is accompanied by very great tenderness along the outer edge of the tibia. Occasionally one sees this tenderness so great that the patient begs that the bed-clothes may be kept off his limbs by a guard. On rare occasions one sees some swelling and even edema of the tissues over the painful shins. I have notes of one case in which this was noted during several relapses.

The exact pathology of the condition is not known. It has been attributed to a periostitis, and some writers have described microscopic changes in portions of the tibial periosteum removed for examination.

"To decide the question whether objective changes are to be found in the tibiæ in trench fever and other febrile diseases associated with tibialgia, and whether such changes are due to the disease or whether they were present before, Burchard[1] made an *x*-ray examination of a number of cases of trench fever and other conditions. Of 32 cases of pure quintan fever 22 had well-marked spontaneous pains in the tibiæ; 3 complained of pain on pressure only; 6 had diffuse pain in the legs; only 1 had no pain whatever in the legs. In almost all these cases the *x*-rays showed a more or less well-marked periostitis in the diaphyses of the tibiæ, less frequently in the fibulæ and occasionally also in the bones of the forearm. The severity of the pain was by no means always in proportion to the periostitis present. The patients complained of severe pain when there were little or no changes visible, and, on the other hand, a patient in whom definite periosteal changes were present did not complain at all. The skiagrams showed that the periosteum alone was affected. Similar lesions were found in 14 cases of trench fever, with an atypical temperature chart. An examination was

[1] Med. Klin., Berlin and Wien, 1918, xiv, 810–812.

then made of 37 soldiers who had been sent to the *x*-ray department for wounds or diseases unconnected with pains in the legs and in about half the cases identical changes were found in the periosteum. A comparison of the three groups of cases showed a striking frequency of periosteal changes in quintan fever and other febrile diseases accompanied by tibialgia. On the other hand the skiagrams did not show anything characteristic, so that the supposition that periostitis was a consequence of the infectious disease was improbable. Burchard thinks it much more probable that the periostitis had been in existence before and that the pain was due to the supervention of the infectious disease!"[1]

J. Plesch[2] protested against the view held by many that shin pains was a *sine qua non* for the diagnosis of trench fever. He thought that probably marching with heavy kits made the tibia a *locus minoris resistentiæ*, and any affection such as influenza, enteric, malaria, relapsing fever or gonorrhea may cause pain here. He confirmed Queckenstett's observations that such pains often followed vaccination for enteric, smallpox or cholera.

All the same I think that few clinicians of experience will now deny that the shin pains are peculiarly common and agonizing in trench fever, more so, indeed, than in any other infection.

The pains are nearly always worse at night and are described variously as aching, burning, dragging, etc.

I quite agree with the above writers that the probable reason why the shins are so often attacked is that the heavy marching has caused some fibrositis here and then the infection or toxemia attacks this damaged area. In support of this view one may cite the fact that trench fever patients constantly tell us they get pain in any old wound site, fracture or strained joint or tissue. In the late stages these cases are often diagnosed as "myalgia." Captain Chevasse and Marr[3] independently examined many cases of "myalgia" and the former believed that 43 per cent. were really trench fever and the latter 70 per cent. and Col. Soltau would put the figure as high as 80 per cent. As already stated I found that 15 per cent. of very

[1] Medical Supplement, November 1, 1918.
[2] Samml. klin. Vortr., Leipzig, 1918, Nr. 745–6; Inn. Med., Nr. 251–2.
[3] Letter of Col. Soltau, Lancet, December 28, 1918, p. 893.

late cases of myalgia studied in England were probably of this nature and even still had some fever.

Some writers believe, however, that the pains are rather of central than peripheral origin. Thus Sir G. Sims Woodhead[1] considers them as being referred and due to excitation of nerve cells in the spinal cord.

2. *Circulatory Symptoms.* During the fever the pulse rises in proportion to the temperature. Accurate watching of the heart in this state of the disease often reveals a temporary displacement of the apex to the left. Such may be seen in any infection and there is no evidence that the virus of trench fever in any way specially attacks the heart muscle or its membranes.

But functional disturbance of the heart is very common after trench fever. In an inquiry into the cardiac manifestations of the disease, J. Fischer[2] found that among 807 patients, 8 per cent. complained of symptoms, such as pain and oppression in the left side of the chest, palpitation and dyspnea, and that all these patients had objective signs, such as rapid pulse, a raised blood-pressure (up to but not beyond 160 mm. Hg.), arrhythmia, mainly respiratory, slight cardiac enlargment and a systolic murmur at the apex or over the pulmonary artery. Patients never showed the acute cardiac failure or vasomotor paralysis seen in other acute infections. Further, the arrhythmia was never of a type to justify a diagnosis of myocarditis. He thought the cardiac disturbances were not myocardial, but nervous. They occurred in patients of weakly and poor muscular development and predisposition was probably a factor in their development. Fortunately trench fever is not a fatal illness, and hence we have no postmortem evidence of the actual state of the heart muscle, but clinically the condition is suggestive rather of a nervous than of an organic nature.

Again it must be remembered that trench fever is the commonest of all infections at the front, and hence many cases of "D. A. H." will naturally give a history of it. The American Trench Fever Commission in their experimental work selected only men of fine physique, and in no instance did they find that any "D. A. H."

[1] British Med. Jour., May 25, 1918, p. 592.
[2] München. med. Wchnschr., 1918, lxv, 73-75.

occurred after the infection was over. Occasionally the syndrome was detected, but it was always found that the infection was still present, and when this finally disappeared so did the circulatory symptoms. It should be noted in this relation that the staff of the special heart hospital at Colchester report that slight fever is often present in trench fever. "D. A. H." is probably cardiac neurasthenia, and it is easy to see how such would be intensified by any infection, and hence we get the history of it so commonly dating from the commonest of all infection, *i. e.*, trench fever. Further, a careful inquiry nearly always shows that the circulatory symptoms preceded the fever and were only intensified by it.

But one would like to repeat that trench fever is often a very chronic condition and to express the opinion that many cases of "D. A. H." are examples of a still present infection. This is very important, for such cases require rest rather than exercise as long as any activity is present.

3. While the chronic infection is present the patients suffer from general malaise and debility. They are weak and below par and easily tired. Their complaints are of being "done up," that their "nerves are all gone," and of "depression." Major J. H. Lloyd[1] found that 50 out of 400 cases of "N. Y. D. N." (not yet diagnosed: nervous) were clear examples of trench fever.

4. *Blood.* The blood picture is variable, but usually there is a moderate leukocyto is during the fever. According to H. Perkins and R. H. Urwick,[2] who made a special study of the hematology of the disease, there is a marked rise in the leukocytes of all kinds at the time of the febrile relapse and a gradual relative rise in the lymphocytes during convalescence. The American Trench Fever Commission found the extreme ranges of the white count was from 3400 to 27,000 and a majority of their cases gave a count of from 13,000 to 17,000.

It must be borne in mind, however, that the white cell count tends to be higher in soldiers than in civilians. Several observers have noted this peculiar fact. Thus Bokelmann and Nassau[3] examined

[1] Lancet, May 10, 1919, p. 791.
[2] Quart. Jour. Med., July, 1918.
[3] Berl. klin. Wchnschr., 1918, lv, 353–4.

the blood of 70 healthy soldiers (officers and men), 59 being of middle age. There was a well-marked increase in the lymphocytes, varying from 25 to 73 per cent. and averaging 43 per cent., with a corresponding diminution in the polymorphonuclear cells. S. Newman[1] found the same thing, as did also D. L. Tate and J. W. McLeod.[2] With this qualification, a rise in the leukocytes may then help in the diagnosis of trench fever as against typhoid, but an absence of this leukocytosis will be of no value.

Professor Duncan Graham tells me that he has found that the chief difference between the blood picture in malaria and in trench fever is that in the former the blood platelets are scanty while in the latter they are numerous. I have not come across any mention of this in the literature.

Last autumn Major D. W. Carmalt Jones[3] described a peculiar condition of cutaneous hyperesthesia that often occurred in trench fever cases. These are of a similar nature to the areas of cutaneous hyperesthesia that have been so minutely described by Sir James Mackenzie and Dr. H. Head as indicative of disease of various organs of the body, only the distribution is different. Major Carmalt Jones examined in a routine manner all the patients coming into a base hospital in France. Definite segmental areas of increased sensibility to pain were found very constantly, corresponding to diseased viscera, but in a number of cases the distribution did not correspond with any viscus. These unusual areas were the margins of the areas supplied by the eighth cervical and first dorsal, the seventh dorsal and all the lumbar segments of the cord.

When all the patients showing such distribution of hyperesthesia were investigated further they were found to be examples of either malaria or of trench fever.

Captain G. E. Sundell[4] in discussing Major C. Jones's findings, confirmed them, but also described areas of anesthesia to pin-prick within the zones supplied by these nerves. These areas were most common on the outer part of the calf, the intrapatellar, scapular and deltoid regions.

[1] Wien. klin. Wchnschr., 1918, xxxi, 1000–4.
[2] Lancet, April 27, 1918, p. 603.
[3] Ibid., October 5, 1918, p. 443.
[4] Ibid., October 19, 1918, p. 538.

I have examined many cases of trench fever in regard to the areas of hyperesthesia and have very often found them present, although I am not so sure of Sundell's areas of analgesia. I have demonstrated the symptom in some cases of "D. A. H." and also of "myalgia," and consider that it is a valuable aid in the detection of chronic and doubtful cases of trench fever.

Such are the chief clinical features of a chronic infection, which in all probability existed in a slight endemic form before the commencement of the war, but which has since then become epidemic to a great degree. As infected men return to surroundings where the body louse is common the epidemic is likely to continue, so that probably we will not only have to deal with many chronic cases for some years to come but will also find new ones cropping up in the poorer and more crowded districts.

THE INCIDENCE OF SYPHILIS AS MANIFESTED BY ROUTINE WASSERMANN REACTIONS ON 2925 HOSPITAL AND DISPENSARY MEDICAL CASES

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AND

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The following report is based upon 2925 Wassermann reactions done as routine on all medical cases admitted to Barnes Hospital and the medical clinics of Washington University Dispensary during the year 1918.

Of these, 675 were hospital patients. This does not include 456 patients admitted to the hospital during the recent influenza epidemic, upon whom routine tests were not done, due to the abnormal conditions existing at that time.

The dispensary cases numbered 2250. This includes patients from the general medical, gastro-intestinal, and neurological clinics. It takes in only a few cases from the tuberculosis clinic, for Wassermanns from this clinic were done, together with tuberculosis complement-fixation tests, in another laboratory, using only a cholesterinized antigen and a different technic from that employed in our series.

The classification of results was undertaken at the suggestion of Dr. Dock, to determine the relative incidence of syphilis as manifested by the Wassermann reaction in four general classes of patients. We have considered, therefore, the following groups, as being representative of four social classes:

Group I. Private pavilion patients; the well-to-do class.
Group II. Pay ward patients; the middle class.
Group III. Free ward patients; the lower (white) class.
Group IV. Colored patients.

In the dispensary cases two groups were considered: white and colored. These again were divided into male and female of each race, and the cases coming from each clinic were grouped together to show the relative frequency of positive reactions from these services.

The technic employed in the tests performed was as follows:

Three antigens were used: an alcoholic extract of syphilitic liver (1 to 10 dilution); a cholesterinized alcoholic beef heart extract (1 to 20 dilution); and the acetone insoluble lipoid antigen of Noguchi (1 to 20 dilution). The various antigen doses were in each instance determined by previous titration. A serum control was run on each test, 0.1 c.c. freshly inactivated patient's serum was added to each of the four tubes set up, 1 c.c. complement—fresh guinea-pig serum, diluted 1 to 20—and 1 c.c. salt solution. The tubes were shaken and incubated one hour at 37.5°, dry heat. With the incubation an amboceptor titration was also made and one and a half times the unit of amboceptor thus determined was used as the dose in the final titration. One cubic centimeter $2\frac{1}{2}$ per cent. suspension of sheep cells was used in both amboceptor titration and the hemolytic system. After adding amboceptor and sheep cells, the tubes were shaken a second time and again incubated for one hour. The results were read immediately.

The following controls were also set up:

1. A known positive serum.
2. A known negative serum.
3. A control on each antigen.
4. A control on the hemolytic system.
5. A control on the sheep corpuscles.

Reports were made on each antigen, using the symbols +, ++, +++, and negative.

All tests were done by one of us (McNitt).

In grouping the Wassermann results for this survey, we have separated into one group all reactions +4 in all antigens; into another those +4 in the cholesterin antigen with strong reactions in one or both of the syphilitic liver and Noguchi antigens, which we have called "strongly positive;" while a few incomplete reactions with the cholesterin antigen, also giving weak fixation with one or both of the other two antigens, were classed as "weakly positive."

The cases giving reaction with the cholesterin antigen alone were also grouped separately. A few reports were returned with negative blood, but positive spinal fluid reactions. There was also a small number of cases giving no blood reaction, but having unquestionable syphilis.

Table I shows the cases grouped under the headings described as regards the Wassermann reaction, and also separated into four classes: Private patients, pay ward patients, free ward patients, and colored.

TABLE I.—INCIDENCE OF SYPHILIS IN 2925 HOSPITAL AND DISPENSARY CASES BY CLASSES

Wassermann result.	Hospital—675 Cases.								O.-P. D.—2250 Cases.			
	Private patients. 144 cases.		Pay ward. 380 cases.		Free ward. 91 cases.		Colored. 60 cases.		White. 1777 cases.		Colored. 473 cases.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
4+ all antigens	3	2.0	16	4.2	11	12 0	7	11.6	109	6.1	84	17.7
Strongly +	2	1.4	11	3.0	3	3.2	7	11.6	50	2.8	53	11.2
Weakly +	..	..	..	..	..	..	..	..	6	0.3	3	0.6
4+ cholesterin	2	1.4	12	3.2	2	2.1	3	5.0	78	4.3	46	9.7
3+ cholesterin											17	3.6
2+ cholesterin	3	2.0	5	3.8	5	5.3	3	5.0	66	3.7		
1+ cholesterin												
Pos. sp. fl. neg. blood	2	1.4	3	0.8	0	..	0	..	4	0.2	0	
Total number with pos. Wassermann	12	8.3	47	12.6	21	23.0	20	33.0	313	17.6	203	42.7
Estimated incidence of syphilis	9	6.3	52	13.6	18	19.8	18	30.0	282	15.9	192	40.5
Neg. Wass. pos. lues	0	..	9	2.3	..	..	1	1.6	28	1.6	4	0.8
Neg. Wass. lues sus.	3	..	15	..	4	..	7	..	104	..	44	
Negative	129	..	309	..	66	..	32	..	1332	..	222	
Totals	144	..	380	..	91	..	60	..	1777	..	473	

In figuring the percentage of positive reactions in each group, all giving a positive test were included. As will be discussed later in this report, the weak cholesterin positives are, when not substantiated by clinical evidence, doubtful proof of the existence of syphilis. In order to obtain a more exact estimate of the incidence of syphilis in each class of patients, therefore, only those cases having definite clinical evidence of syphilis were included among those giving Wassermann reaction 3+ cholesterin or less. Also cases having syphilis, but giving negative reactions are included. The figures thus obtained

are shown under the heading "estimated incidence of syphilis" in Table I.

It will be seen that 6.3 per cent. of the private patients, representing the upper social class, are estimated as having syphilis. Relating the results obtained in the other classes to this figure, the percentage for pay ward patients is about twice as high; for free ward patients, three times as high; and for colored patients, five times as high. Among the white dispensary patients, socially on about the same footing as the free ward patients, 15.9 per cent. are estimated as having syphilis, a figure somewhat lower than the free ward incidence. The colored dispensary patients showed more than six times as much syphilis as private hospital patients.

To draw exact conclusions from such figures is impossible. But it is felt that they give an indication of the relative incidence of syphilis among the four social and racial groups considered.

The literature gives little information on the incidence of syphilis as shown by Wassermann reaction among the well-to-do class.

In order to ascertain what percentage of cases giving positive reactions gave also clinical evidence of syphilis, and in what percentage—no such evidence was found in the case records—Table II was constructed.

The Wassermann results were grouped as before. Under the heading "*Clinically Negative*" were placed all cases giving no indication in the history or physical examination of syphilitic infection. A history of miscarriages, stillbirths, or childless marriage excluded from this group. So, also, any history of a penile sore, whether typical or manifestly atypical in description, excluded.

Clinically positive cases include all giving definite history of infection, with or without treatment, definite physical evidence of syphilis, or both.

Cases which could not be diagnosed clinically, but gave some hint as to the possibility of syphilitic infection were grouped together as "Clinically Suspicious." Many of these cases gave a history of a primary "sore;" a few gave history of treatment. A history of miscarriages, stillbirths or childless marriage put a case in this group.

In drawing conclusions from this table, it must be remembered that histories, at best, are inaccurate regarding syphilitic infection,

either because the patient withholds the truth, is ignorant of infection, or the examiner fails to ask specific questions. This is particularly true of dispensary histories. When no mention was made of specific history or physical findings, the case, if giving a positive Wassermann, was classed as "Clinically Negative."

Considering the cases +4 in all antigens and those strongly positive, it is seen that about 15 per cent. gave no clinical evidence of the disease. A still higher percentage of clinically negative cases is found among cholesterin positives, rising as the reaction becomes weaker. There may be several causes for this increase.

1. Errors in history taking. This, however, we may assume to be about equal in all groups, and probably has little influence.

TABLE II.—TO SHOW THE RELATION BETWEEN THE WASSERMANN RESULT AND CLINICAL EVIDENCE OF SYPHILIS

Wassermann result.	Number cases.	Clin. neg.	Clin. neg. per cent.	Clin. susp.	Clin. susp. per cent.	Clin. pos.	Clin. pos. per cent.
4+ all antigens . .	230	39	16.9	51	22.5	140	61.0
Strongly + . . .	126	19	15.1	30	23.7	77	61.2
Weakly + . . .	8	1	12.5	3	37.5	4	50.0
4+ cholesterin . .	143	34	23.8	45	31.5	64	44.7
3+ cholesterin . .	21	7	33.3	11	52.3	3	14.3
2+ cholesterin . .	35	13	37.3	15	42.8	7	19.9
1+ cholesterin . .	42	17	40.5	22	52.2	3	7.3
Neg. blood + sp. fl.	9	0	....	0	....	9	100.0
Total pos. . . .	614	130	21.1	174	28.4	310	50.5
Neg. blood . . .	219	0	0	177	81.0	42	19.0

2. A greater number of false positives among the weak reactions than among the strong. This is no doubt true and accounts in a large part for the differences in percentages noted. Only 7.3 per cent. of the 1+ cholesterin cases were clinically positive, 44.7 per cent. of the 4+ cholesterin cases, and 61 per cent. of those giving strongly positive reactions. All of the clinically positive 1+ cholesterin cases were treated. A more careful analysis of the 22 clinically suspicious cases shows that 3 were negative on repetition, leaving 19 done only once. Of the 17 clinically negative cases, 3 were negative on repetition and 4 were negative after provocative treatment, leaving 10 in which the reaction was not repeated.

In the absence of good clinical evidence of syphilis, these repeated cases are undoubtedly not syphilitic and those not repeated were probably not syphilitics.

Of the 2+ cholesterin reactions 19.9 per cent. were clinically positive; all had received treatment.

Fifteen were "suspicious clinically," 5 of these were negative on repetition. One gave the same reaction on repetition. Two were positive on former tests, 5 were negative on repetition, and the remaining 7 had only one test done.

Of the 13 clinically negative cases, 5 gave negative reactions on repetition. The remaining 8 were not retested.

TABLE III

Wassermann result.	Number.	White males.	White females.	Colored males.	Colored females.	Med. I.	G. I.	Nerve.	Chest.
4+ all antigens	193	66	43	42	42	114	35	40	4
Strongly +	103	25	25	29	24	65	15	22	1
Weakly +	9	4	2	2	1	5	1	2	1
4+ cholesterin	124	34	44	17	29	64	23	35	2
3+ cholesterin } 2+ cholesterin } 1+ cholesterin	83	38	28	5	12	47	12	22	2
Sp. fl. only	4	2	2	0	0	1	1	2	0
Total pos. Wass.	516	169	144	95	108	296	87	123	10
Neg. Wass. pos. lues	32	20	6	4	2	14	2	16	0
Negative	1702	664	774	101	163	907	442	343	10
Totals	2250	853	924	200	273	1217	531	482	20
Pos. Wassermann	23%	20%	16%	48%	40%	24%	16%	26%	50%
Estimated incidence of syphilis	21%	18%	14%	48%	36%				

Summarizing the cases giving 1+ and 2+ cholesterin reactions, we can safely say that of 77 such cases, 10 had syphilis, 15 were not syphilitic as repeated tests were negative, and the remaining 52 probably did not have syphilis.

Of the cases 3+ with the cholesterin antigen, 3 had syphilis, 3 were negative on repetition and did not have syphilis, while 15 (6 clinically negative and 9 suspicious clinically) had only one test done.

Of the 4+ cholesterin cases, 64, or 44.7 per cent. had syphilis clinically. Two of the 34 clinically negative cases were positive on repetition; one was negative after provocative treatment. All other cases were only tested once.

We cannot draw any conclusions from these figures, when the record and not the patient is our only means of information. They emphazise the importance of careful history taking and of doing

repeated tests on cases giving reactions with the cholesterin antigen only. In this way alone can we say whether or not such reactions, in the absence of clinical evidence of syphilis, are specific.

Table III shows the percentage of positive Wassermann reactions in the sexes and races among 2250 out-patient cases. An estimate was also made of the probable incidence of syphilis by disregarding the cases giving positive cholesterin reactions less than 4+, except those clinically positive, and including cases having syphilis but giving negative Wassermann reaction

Table III also shows the percentage of positive reactions and estimated incidence of syphilis in the cases from the general medical clinic (Med. I), gastro-intestinal clinic (G. I.) and nerve clinic.[1]

C. N. S. Syphilis. One hundred and thirty-four cases of neurosyphilis were encountered in our total series, or 20 per cent. of all cases giving positive reactions (668) or definite evidence of syphilis without positive Wassermann (42). This figure agrees with the estimation made by Fordyce that 20 per cent. of all syphilitics would on careful examination be shown to have nervous system involvement. Parkin and Cornwall feel that 30 to 40 per cent. of those infected have syphilitic foci in the nervous system.

Of 13 cases giving reactions 3+ or less in the cholesterin antigen alone, 8 were clinically positive. It is well known that the cholesterin antigen is particularly valuable in cases of neurosyphilis.

Twenty-six cases gave negative blood Wassermanns, 4 of these gave a positive spinal fluid Wassermann; 6 had negative spinal fluid reactions. Of 22 negative blood reactions, including 6 with negative spinal fluid also, only three gave no history of treatment, 19, or 86.5 per cent., were treated cases.

[1] Patients coming to the tuberculosis clinic had routine tests done, in conjunction with the complement-fixation test for tuberculosis, in a separate laboratory, using a different technic from that employed in our series. A cholesterinized beef heart antigen alone was used, of a less sensitive titer than ours.

I am indebted to Doctor J. J. Singer, physician-in-charge of the Tuberculosis Clinic of the Washington University Dispensary, for permission to use the following figures. The tests were performed under the direction of Doctor George Ives, by Miss D. Lamb:

CHEST CLINIC.

Cholest. antigen.	Number.	Per cent.
++++	102	11.3
+++	36	4.1
++	35	3.9
+	36	4.1
Negative	684	
Total	893	23.4 positive.

Spinal Fluids. Eighty-six spinal fluids were tested; 28 were strongly positive and 7 were positive in the cholesterin antigen only, though all cholesterin positives had clinical neurosyphilis. Thus 35, or 39.7 per cent., of the spinal fluids tested gave positive Wassermann reactions. Fifty fluids gave negative reactions. Of this number, 6, or 7 per cent., had an increased cell count with positive globulin reaction, all in cases of clinical neurosyphilis; 13, or 16.2 per cent., were normal on microscopic and chemical examination though all had clinical C. N. S. syphilis, only one being questionable. Of the 31 remaining cases, 4 had strongly positive blood reactions, in 5 there was a cholesterin reaction only; while in 22 the blood test was also negative. In these 22 cases, 3 were luetic, 8 non-luetic and 11 questionably luetic clinically.

TABLE IV.—134 CASES OF C. N. S. SYPHILIS AMONG 2925 HOSPITAL AND DISPENSARY CASES

Wassermann result.	C. N. S.		Tabes.		Tabo-paresis.		Paresis.		Meningitis (luetic).		Total.
	Clin. pos.	Clin. ?	Clin. pos.	Clin. ?	Clin. pos.	Clin. ?	Clin. pos.	Clin. ?	Clin. pos.	Clin. ?	
Strongly + . .	38	2	18	..	2	..	8	..	2	..	70
4+ cholesterin .	15	1	3	..	1	..	4	1	..	..	25
3+ cholesterin .	2	3	..	..	..	..	..	..	..	..	4
2+ cholesterin .	2	0	..	..	..	..	1	..	..	..	3
1+ cholesterin .	2	2	..	..	..	..	1	..	..	..	5
Pos. sp. fl. neg.	2	..	1	..	..	..	1	..	..	..	4
Neg. Wass. . .	12	..	8	..	1	..	1 (treated)		..	..	22
Total . . .	73	8	30	0	4	0	16	1	2	0	134
Clin. pos. cases having positive Wassermann .	83.5%		73.3%		75%	..	93.7%	..	100%		

Diabetes. There were 33 cases of diabetes; 7 gave positive Wassermann reactions; 3 of this number were strongly positive and admitted infection; one other was 4+ in all antigens but no history was obtained as the patient was in coma on admission. Of the other 3 cases, one was 4+ cholesterin and on repetition 1+. This patient gave definite physical evidence of syphilis. One case gave a 2+ cholesterin reaction; he admitted infection and treatment. The last case gave a 3+ cholesterin Wassermann, denied infection, but admitted gonorrhea. The spinal fluid was negative. The blood Wassermann was not repeated.

Therefore, out of 7 positive Wassermanns among 33 diabetics only one had an unexplainable weak cholesterin reaction.

Malaria. Eleven cases of malaria gave 4 positive reactions, or 36.5 per cent. One case of tertian malaria was strongly positive and remained so after malarial treatment. Her Wassermann was still 3+ cholesterin six months after her malarial infection, which did not recur.

Two cases gave strongly positive reactions while in the acute stage of the tertian malarial infection. One was completely negative fifteen days later without any treatment except quinine. The other became 1+ cholesterin one month later with the same treatment. Neither case gave any clinical evidence of syphilis. It seems probable, therefore, that these 2 cases gave strongly positive reactions due to malarial infection and not to syphilis. A more detailed report of these cases is given in the complete paper.

Conclusions. Two thousand nine hundred twenty-five hospital and dispensary patients were subjected to a routine Wassermann test during the year 1918. From a detailed examination of the results obtained the following conclusions seem justifiable:

1. The incidence of syphilis as shown by the Wassermann reaction was lowest among the well-to-do, about twice as high among the middle class of society, represented by the pay-ward patients, and about three times as high among the lower social class, or free-ward patients. The incidence of syphilis among colored patients was about six times that among private patients.

2. About 15 per cent. of cases giving strongly positive reactions gave no clinical evidence of syphilis. This percentage increases with the cholesterin positive cases, indicating that a certain number of cases giving weakly positive Wassermann reactions with the cholesterin antigen only did not have syphilis.

3. The percentage of clinically positive syphilis is highest in the strongly positive group (61 per cent.) and lowest in the +1 positive cholesterin cases (7.3 per cent.).

4. Weak reactions with the cholesterinized antigen are of value only when there is a definite clinical evidence of syphilis, in treated cases, or in cases of neurosyphilis.

5. Of 853 white males, 30 per cent. gave positive Wassermann

reactions; of 924 white females, 16 per cent. were positive. Among colored patients 48 per cent. of 200 males and 40 per cent. of 273 females gave positive Wassermann reactions.

6. Among 7 cases of diabetes giving positive Wasserman reactions, only one did not give clinical evidence of syphilis.

7. Of 4 cases of malaria giving positive Wassermann reactions it seems probable that 2 of the positive reactions were due to malarial infection and not to syphilis.

TRANSFUSION OF BLOOD IN PERNICIOUS ANEMIA: REPORT OF AN INTERESTING CASE

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This paper is not an attempt to solve the problem of the genesis of pernicious anemia, although some of the views bearing on this phase of the subject are briefly discussed. Neither can it be claimed to offer anything novel by way of treatment. The chief aim has been to validate the claim advanced by certain writers that transfusion offers more for progressive pernicious anemia than any other form of treatment, by a survey of the clinical results obtained principally by surgeons during the decade last past, Werner Schultz[1] having given a complete bibliography up to 1910.

Some of the gaps in our knowledge of this obscure disease promise to be filled from the field of comparative pathology. For example, Seyderhelm[2] has demonstrated that injected extracts of the larvæ of the fly, *Estrus equi*, which is found in the walls of the horse's stomach, produce symptoms characteristic of the severer types of anemia.

Seyderhelm has also shown that the hemolytic lipoids derived from the fly larvæ do not cause the symptoms of severe anemia, but rather the non-hemolytic fragments of larval substance.

If the foregoing view be correct the theory of defective hemogensis, which is held by Henry, Rindfleisch, MacKenzie and other hematologists as the primary cause of pernicious anemia, cannot be altogether abandoned, although injury to the hematopoietic organs, so far as scientific evidence is concerned, occupies a less conspicuous

[1] In Crawitz, Klinische Pathologie des Blutes, Leipsic, 1911, p. 381.
[2] Arch. f. exper. Path. u. Pharmakol., 1918, lii, 253.

place in the etiology of this disease than toxic hemolysis. It would appear to be clear that the blood picture presented by pernicious anemia reflects an effort of the blood-generating organs to compensate the unusual hemolytic activity of unknown origin. In this connection the abnormally large pigment depositions to be found, more particularly in the liver and spleen, at necropsy in this disease, confirm the highly fatal blood destruction which characterizes the complaint. The fact that defective lipoid metabolism results in diminished hemolytic properties of the whole blood should be also recollected.

Additional evidence of the pernicious activity of hemolytic agents in Addisonian anemia is afforded by the presence of an undue quantity of urobilin in the stools. Moreover, Sellards and Minot[3] have shown that hemoglobinuria follows the subcutaneous injection of hemoglobin in amounts incapable of producing the appearance of urinary blood pigment in other types of anemia. Eppinger[4] contends that the excessive erythrocytic destruction, which takes place in the spleen (the exact site of the hemolysis being the splenic pulp) is due to the anatomical changes presented by this organ in pernicious anemia. In those anemias of the pernicious type, which are due to known causes, *e. g.*, malignant tumors, "hemolytic toxins are possibly responsible for the blood condition" (Kullmann[5]). Krehl[6] and others direct attention to an increased regeneration of erythrocytes in pernicious anemia, which accounts for the escape of immature red cells, including the characteristic megaloblasts, into the circulation.

Sajous[7] states that hemolysis occurs whenever toxins, either endogenous or exogenous, appear in the blood in quantities sufficient to excite a defensive reaction. He continues: "The antibodies then attack not only the toxics but the erythrocytes as well." H. A. Christian[8] concludes that in severe cases of Addisonian anemia the renal function is disturbed much as in advanced chronic nephritis. This seems to be either a toxic or nutritional disturbance in renal cellular activity.

[3] Jour. Med. Research, 1916, xxxiv, 469.
[4] Berl. klin. Wchnschr., 1913, c, 2409.
[5] Ztschr. f. klin. Med., p. 3.
[6] The Principles of Clinical Pathology, 1916, p. 148, J. B. Lippincott Co., Phila.
[7] Index Supplement, p. 133.
[8] Arch. Int. Med., October, 1916.

On the basis of modern researches and sound data, prophylactic measures are attracting professional attention, after ascertaining the presumable etiological factor in the given case. For example, certain observers attach prime importance to oral sepsis as the cause of the disease; this, however, produces a secondary type of anemia.

L. F. Barker and G. P. Sprunt[9] have emphasized this phase of the problem, recommending the removal of all discoverable foci of infection; they further advise an abundant, roborant diet, arsenic, the exhibition of hydrochloric acid immediately after meals and of pancreatin and calcium carbonate three hours after each meal. I have mentioned the main details because of their claim that under this treatment splenectomy and transfusion of blood were not found necessary in a special group of cases.

Leyton,[10] affirms that massive transfusions of blood offer the greatest chance of improvement to sufferers from pernicious anemia, but, he adds, "Any error in the technic may be followed by a fatal result." Archibald[11] transfused a series of 20 cases at the Mayo Clinic, with marked immediate benefit in 69 per cent., while among 14 cases deemed unsuitable for splenectomy similar improvement was noted in 50 per cent. Vogel and McCurdy[12] regard the transfusion of physiologically unaltered blood as a palliative treatment of great promise. Kimpton,[13] who transfused upward of fifty cases, is of the opinion that transfusion offers more for this disease than any other form of treatment.

It is highly probable, at least, that transfusion of blood in this disease owes its beneficial effects principally to stimulation of the antihemolytic properties of whole blood, although possibly also to some extent to its power to increase the activity of the bone-marrow. Obviously, anything that will tend to evoke a strong defensive reaction against the special hemolytic factors will prove useful.

Turk,[14] however, believes that the added blood, combined with some putative hemolytic present, thus protecting the bone-marrow, allows it opportunity to retrieve some of the lost cells.

[9] New York Med. Jour., June 9, 1917.
[10] Practitioner, London, March, 1917.
[11] St. Paul Med. Jour., February, 1917.
[12] Arch. Int. Med., 1913, xii, 707.
[13] Boston Med. and Surg. Jour., May 14, 1918, No. 11, clxxviii, 351.
[14] Vorlesungen über klin. Hamatologie, Vienna, 1912.

Case Report.—A. F., aged sixty five years, retired merchant, of healthy parentage, began to decline in health about March 1, 1918, growing weak and pale as well as dyspneic. Anorexia soon was complete, and there were belching, abdominal distress, a tired, languid feeling, loss of physical strength and marked mental hebetude.

On physical examination nose, throat, eyes, ears normal; had several decayed teeth which were extracted. There was a marked mitral murmur. May 1, 1918, went to Atlantic City for three weeks, but became progressively weaker during his stay there, so that he had to be semoved to his home, not being able to move about without assistance.

May 19, blood count showed: Hemoglobin, 20 per cent. (von Fleishel); erythrocytes, 720,000; leukocytes, 3400. Differential count: polymorphonuclear neutrophiles, 72 per cent.; small lymphoctes, 23 per cent.; large lymphocytes, 2 per cent.; transitional, 2 per cent.; mast-cells, 1 per cent.

Marked anisocytosis and poikilocytosis; megalocytes predominate; polychromatophilic degeneration; very few erythroblasts.

Upon this laboratory evidence and the clinical symptoms and course pernicious anemia was diagnosed. I was called to see the patient May 22 by the attending physician, Dr. S. Shahan, who concurred in the diagnosis and gave an unfavorable prognosis, based upon the patient's feeble condition. Transfusion was performed May 24 by Dr. A. J. Rubenstone, 500 c.c. of whole blood from the patient's son, which was found compatible by the Roux Turner method, being transferred. This was followed later in the day by slight chill, rise of temperature to 102° F., and marked restlessness, from which the patient quickly recovered after injecting several doses of adrenalin chloride and atropin. Rapid clinical improvement followed; color improved markedly, patient asked for food, and within one week the patient was out of bed.

June 3, 1918. The patient had resumed his normal activities and a blood count now showed: Hemoglobin, 40 per cent; erythrocytes, 2,050,000; leukocytes, 5400. Differential count: polymorphonuclear neutrophiles, 57 per cent.; small lymphocytes, 34 per

cent.; large lymphocytes, 4 per cent.; transitional, 1 per cent.; mast cells, 1 per cent. Some anisocytosis; megalocytes predominate; some poikilocytosis.

The cardiac murmur had entirely disappeared and improvement from then on was steady. Arsenic and iron injections hypodermically, which he had received since transfusion every other day, were now suspended. The patient was next seen November 19, 1918, and appeared perfectly well. Indeed, he stated that he had "not felt so good for fifteen years."

November 19. Blood count: Hemoglobin, 70 per cent.; erythrocytes, 3,280,000; leukocytes, 5000. Differential count: polymorphonuclear neutrophiles, 63 per cent.; small lymphocytes, 37 per cent.; some anisocytosis and megalocytosis. The patient continued to do unusually well until January 1, 1919, when he slowly developed a relapse. A little pallor, a little cardiac palpitation, dyspnea and anorexia appeared.

The blood count January 23 showed: Hemoglobin 60 per cent.; erythrocytes, 1,700,000; leukocytes 3600. Differential count: polymorphonuclear neutrophiles, 72 per cent.; small lymphocytes, 26 per cent.; large lymphocytes, 2 per cent. Megalocytosis, reds stain intensely.

March 8. Transfusion repeated. Almost no reaction followed, but improvement was immediate, although somewhat slow and gradual. He has now, May 15, 1919, returned to the same state that he presented in November, 1918. Blood count: hemoglobin, 65 per cent.; erythrocytes, 3,160,000; leukocytes, 6000. Differential count: polymorphonuclear neutrophiles, 62 per cent.; small lymphocytes, 33 per cent.; large lymphocytes, 3 per cent.; transitional, 2 per cent. Patient's general condition is now remarkably good, just one year after the first transfusion, being able to attend to duties that he has not performed for the past ten years.

It was the surprisingly brilliant result obtained in this case, that impressed me with the need for a careful survey of the recorded experiences of clinicians and surgeons with this procedure during the decade last past. The following table sets forth the main results of my collective investigations.

Author.	Reference.	Number of cases.	Number of transfusions.	Method.	Results.	Remarks.
L. H. Hemplemann	Int. Med. Jour., 1910, xvii, 316	1	1	Direct transfusion	"Improvement lasting a short time."	
A. M. Fauntleroy	U. S. Naval Med. Bull., 1911, v, 47	2	4	Vein to vein	Temporary remissions.	
O. Hannsen	Verhandl. d. Cong. f. inn. Med., 1911, xxviii, 141	14	45	Intravenous injection of defibrinated blood	Remissions in 8 cases; doubtful benefit in 2 and none in 4	First transfusion at times negative; later ones effective.
E. Elliot, Jr.	Ann. Surg., 1911, liii, 131	1	1	.....	Remission over 2 months.	
G. Woolsey	Ann. Surg., 1911, liii, 131	2	2	Artery to vein	Decided remission in 1 case; other sl. improved	First case infected with malaria.
J. A. Hartwell	Med. Rec., 1911, lxxvii, 1005	1	4	.....	Remissions lasting a few weeks.	
D. Bovaird, Jr.	Med. Rec., 1911, lxxix, 239	3	3	Direct transfusion	Remissions in 2	Malarial infection resulted in 1 case.
Bennecke	München. med. Wchnschr., 1912, lix, 1571	4	4	Vein to vein	Negative	All in terminal stage.
B. M. Bernheim	Jour. Am. Med. Assn., 1913, lxi, 268	2	5	.....	1. Repeated remissions; 2. Negative.	
H. M. Vogel and U. F. McCurdy	Arch. Int. Med., 1913, xii, 707	4	7	.....	Temporary remissions after first injections.	
E. Lindemann	Jour. Am. Med. Assn., Mar. 28, 1914	19	40	.....	11 remissions; 8 unimproved.	
A. H. Noehren	Buffalo Med. Jour., 1914-15, lxx, 347	1	1	.....	Died 11 days after transfusion.	
R. Ottenberg and E. Libman	Tr. Assn. Am. Phys., 1915, xxx, 149	25	32	.....	Remissions in 14 cases, 11 not benefited; duration: 1, 3 mos., 3, 6 or more mos.; 3, a year or more; 3, over 2 years.	
J. H. Gibbes	South. Med. Jour., 1915, viii, 48	1	2	.....	Remission.	
W. V. Brem	Jour. Am. Med. Assn., July 15, 1916, p. 190	24	82	Citrated	.....	Reaction in 25 per cent.; 1 patient received 20 transfusions.
J. W. Churchmann	Jour. Am. Med. Assn., Sept. 9, 1916	1	Several	.....	Marked remission	Developed syphilis from son.
F. W. Birtch	California State Jour. Med., June, 1916, p. 240	2	..	.....	1 remission.	

H. E. Mileny, W. W. Stearns, S. G. Fortuine, R. M. Ferry	Am. Jour. Med. Se., 1917, cliv, 733	40	164	Both citrated and whole blood	"Spontaneous remissions definitely hastened in many cases."	
H. Z. Giffin . . .	Jour. Am. Med. Assn., Feb. 10, 1917, p. 429	19	..	.....	Marked gain in 8; sl. in 6; no improvement in 4	Transfusions were preparatory to splenectomy.
R. D. McClure and G. R. Dunn . .	Johns Hopkins Hosp. Bull., Mar., 1917, p. 99	17	64	.....	Beneficial, 53 per cent.; no benefit, 35 per cent.; harmful, 10 per cent.	7 to 10 per cent. gave reactions.
A. E. Stamfeld . .	Lancet, London, March 31, 1917, p. 484	9	..	.....	Marked remissions in 4; less marked in 3.	
R. G. Larabee . .	Boston Med. and Surg. Jour., April, 1917, p. 553	6	8	.....	Remissions in 4 cases lasting from 2 to 11 months.	
C. R. Minot and R. I. Lee	Boston Med. and Surg. Jour., 1917, elxxvii, 761	46	89	.....	Marked remissions in 9; definite but slow in 20; 17 unimproved	Reactions followed 34 transfusions.
C. G. Heyd . . .	New York Med. Jour., 1917, evi, 57	1	1	.....	No remission.	
V. P.W. Sydenstricker, V. R. Mason, and T. M. Rivers . .	Jour. Am. Med. Assn., June 9, 1917, p. 1677	11	49	Citrated.		
O. Leyton	British Med. Jour., April 1, 1916, p. 484	1	2	.....	Remission after first transfusion.	
A. Archibald . . .	St. Paul Med. Jour., 1917, xix, 43	26	46	.....	61 per cent. received distinct benefit.	
C. K. P. Henery . .	Canadian Med. Assn. Jour., 1917, vii, 18	2	..	.....	1 slightly improved; 1 negative.	
E. L. Goar . . .	Texas State Jour. Med., Mar., 1918, p. 388	1	1	Whole blood	Temporary remission.	
V. C. Hunt . . .	Texas State Jour. Med., Sept., 1918, p. 192	123	403	Citrated	Marked remissions in about 60 per cent. with reactions; poor response in 40 per cent. in absence of reactions	Reactions in 94, or 23 per cent.; poor response when no reaction.
E. Sehisler . . .	Jour. Missouri State Med. Assn., 1918, xv, 192	1	3	Citrated	Improvement.	
A. Bloomfield . . .	Johns Hopkins Hosp. Bull., 1918, xxix, 101	26	..	Mostly citrated	Remissions in 51 per cent.; average duration 5½ mos.	
S. W. Sappington .	Hahnemann Monthly, Philadelphia, 1918, liii, 518	13	19	Citrated	Majority developed remissions lasting several mos. up to 16 mos.	
S. Shaham and J. M. Anders	Not published	1	2	Whole blood	2 remissions.	Last remission still holding.
		450	1084			

The totality of 450 cases, in which 1084 transfusions were performed, is large enough to base thereon a fairly accurate estimate of the value of transfusion as a remedial measure. Considerable light has been thrown upon the question of the duration of remissions by transfusion by these observations, although the reports are too often silent on this phase of the effects of the procedure. Of 362 cases in which the result was given, 204, or 56.3 per cent., showed an initiation of remissions. Cases in which the improvement was brief and might have been ascribable to the mechanical effects of the transfusion were not included in the figures representing remissions. It is worthy of note that the average number of transfusions per patient was 2.4, while the extremes ranged from 1 to 20 operations.

Weber[15] Hurter[16] and others have, as a result of personal observation, reached the conclusion that repeated smaller transfusions, *e. g.*, "200 to 500 c.c.," which are free from dangerous reactions, give more satisfactory results than single, massive ones. The series of cases which make up the accompanying table confirm this view. Single transfusions, however, prove sufficient in a certain percentage of cases (11 out of 26, Archibald). The determination of the precise amount of blood to be transferred is a question requiring further study and investigation. Of 185 cases in which the method was mentioned, 172 were transfused with citrated blood.

In this connection Vogel and McCurdy conclude, as the result of their studies that "The enumeration of the reticulated cells by means of the method of vital staining affords a useful means of gauging the hemopoietic activity of the bone-marrow, and by watching the patient's progress in this way the indications for and effects of various therapeutic measures can be well determined and supervised." The intervals in the case of multiple transfusions, must be determined by repeated examinations of the patient's blood, preferably by the method of Vogel and McCurdy, since this is the only trustworthy method of estimating their effect. Obviously, the patient's general condition and subjective sensations must likewise be taken into account.

[15] Deutsch. Arch. f. klin. Med., 1909, xcvii, 165.
[16] Med. Klin., 1911, No. 12.

The splendid results achieved from transfusions by a large number of excellent observers, in an innately fatal disease in which the diagnosis cannot be said to be conjectural, except at an early stage, render it highly expedient to determine their precise field of usefulness. Shall they be employed so soon as the diagnosis of the disease can be made with accuracy in progressive cases? or shall they be limited to the cases that have proved refractory to the arsenical treatment including salvarsan and neosalvarsan, "with results that promise their continued use as the most certain form of therapy in this disease?" [17]

It is believed by a number of competent observers, *e. g.*, Bovaird,[18] Lee, Minot and Vincent,[19] Ottenberg and Libman,[20] and others that when the hemoglobin percentage falls to or below 20 per cent. transfusion of blood offers the possibility not only of averting death; but at times at least of initiating one of the periods of quiescence so characteristic of the disease.

That it is unwise to wait until the average hemoglobin percentage falls as low as 20 per cent. is a conclusion supported by both clinical experience and statistical evidence. Ottenberg and Libman[21] found that the average hemoglobin percentage before transfusion of 14 cases which showed remissions was 27 per cent., "whereas the average of 9 cases which showed no remissions (excluding rapidly fatal cases) was only 20 per cent.

In the case which had reached an advanced stage before the procedure was resorted to, briefly reported above, the effects of the first transfusion were decided and lasted about eight months, and a second transfusion gives promise of an equally favorable result. As a means of establishing a reputation for the procedure, however, the limitation of its use to well-nigh hopeless cases is not promising. The present researches indicate clearly that earlier transfusions in cases showing no tendency to spontaneous remission or as the result of the more usual methods of treatment would yield the best results. Again, remissions are more easily induced in the earlier than the later stages of the disease.

[17] Da Costa's Handbook of Medical Treatment, ii, 21.
[18] Medical Record, February 11, 1919.
[19] Jour. Am. Med. Assn., September 2, 1916, p. 719.
[20] Am. Jour. Med. Sc., July, 1915, p. 36.
[21] Loc. cit.

Transfusion does not prolong the period of remission. Cabot's figures show the quiescent period to be over six months in 165 out of 329 cases, whereas in my series, so far as could be ascertained from available literature, it was somewhat shorter on the whole. On the other hand, this measure easily brings about an increased number of remissions, hence it is not unreasonable to suppose that the total duration of life may be thereby prolonged, as was doubtless the case in many instances included in my table. Evidence exists to show that those examples of the disease which have shown most improvement after transfusion had run a prolonged course as a rule, while the more rapidly progressive cases manifested a feebler remission.

Two methods of administration of defibrinated blood—namely, by intramuscular and intravenous injection—have been advocated, but the results are less satisfactory than those yielded by whole blood. Curtis and David,[22] after making experiments on dogs, consider defibrinated blood unsuitable for human transfusion and Pike, Guthrie and Stewart,[23] and others have found that defibrinated blood on standing a few hours undergoes changes affecting the corpuscles and impairing its nutritive and bactericidal qualities. In view of these facts, and remembering that fresh unaltered blood can, thanks to the recent advances in vascular surgery, be safely transferred from one individual to another, the further use of defibrinated blood is rendered quite undesirable.

It has been suggested to employ antidiphtheria serum in those examples of the disease in which the toxemia predominates and counteracts the action of the arsenic. It seems to me, however, that in many of these cases more favorable results would be obtained from the injection of whole blood after combating discoverable causes. The same remark applies to venesection which has been advised as a palliative measure. Other special methods of treatment have been employed in cases refractory to arsenic and iron therapy, *e. g.*, by the hypodermic use of splenic extract (Maikhailoff) and antistreptococcus and antistaphylococcus serums; but these have not gained an enviable reputation for themselves, and it is unwarrantable to permit them to supersede transfusion of blood, which deserves a more extended trial and promises a far better therapeutic effect.

[22] Surg., Gynec. and Obst., 1912, xv, 476. [23] Jour. Exper. Med., 1908, p. 371.

From an examination of the available literature and personal observation and knowledge of individual cases, I concur in the opinion expressed by Kimpton[24] that the results of splenectomy hardly warrant the operation. This view is based on the assumed facts that transfusion offers quite as much as splenectomy, "with or without transfusion" (Kimpton), and that it obviates immediate deaths. The belief among certain observers that transfusion following splenectomy brings a more steady response than without splenectomy is not borne out by professional experience as a whole.

Rrumbhaar,[25] in a series of the late results of splenectomy in 153 cases, noted a mortality rate of about 20 per cent. and also that, as a rule, the improvement was transient. Moffitt,[26] in an earlier article, states that of 33 cases of splenectomy for pernicious anemia gleaned from the literature, including one under his own observation, "eight died immediately or not long after the operation."

It is obvious that a method of so great promise as transfusion should be more widely adopted as a means of prolonging life. Berheim[27] has reported the interesting case of a man admitted to the clinic of Dr. J. C. Bloodgood, who was transfused four different times from three donors and lived two years after having been given up as lost. In the small percentage of cases in which severe and increasing reactions follow the use of homologous blood, the injections should be discontinued.

Since the technical success of the operation in competent hands is assured both as regards the recipient and donor, it should be repeated with sufficient frequency to avoid the development of an extreme degree of anemia.

The question arises, Have we not arrived at the point at which internists and general practitioners, under whose observation and care pernicious anemia first falls, as a rule, should advise immediate transfusion after an assured diagnosis has been made, during the non-quiescent period, seeing that it initiates a prompt remission in at least 56 per cent. of the cases? This procedure should be, however, supplemented by appropriate hygienic measures and ap-

[24] Loc. cit.
[25] Jour. Am. Med. Assn., 1916, lxvii, 723.
[26] Am. Jour. Med. Sc., No. 6, cxlviii, 822.
[27] Jour. Am. Med. Assn., 1913, lxi, 268.

proved medicaments, and in cases which are refractory to transfusion the usual medical treatment by arsenic, including salvarsan intravenously, and subcutaneous injections of iron, should receive a trial before resorting to other methods of treatment. Finally, the dictum that this measure, when skilfully employed, offers more than any other method of treatment alone, is confirmed by the results of my collective studies.

My sincere thanks are due Dr. S. Shaham, for permission to publish the report of his interesting case, and also Dr. A. J. Rubenstone, for certain details connected with his two transfusions.

DISCUSSION

Dr. Emanuel Libman, of New York, said that he thought that transfusion properly carried out was without risk. The difficulties came from hasty testing of the bloods, transfusing too large an amount of blood, or technical errors in doing the transfusion.

In the paper by Dr. Ottenberg and himself it had been shown that the transfusion does not influence the achylia nor change much the symptoms due to disease of the nervous system or of the tongue. These phenomena were due to the same toxic cause that produced the anemia and were not dependent upon the latter.

He drew attention to the large amount of valuable information concerning the value of transfusion and splenectomy contained in the papers by Drs. Minot and Lee. From his own more recent studies he could not convince himself that transfusion would start a remission unless such remission would have later occurred spontaneously. In other words the transfusions seem to hasten the beginning of remissions and seem to make them last longer. Even if one were to conclude that transfusions did not prolong life much the patient certainly was in much better condition during the time that he lived.

This measure is not to be thought of during a remission, but in the progressive stage of the disease, and it should be resorted to before the hemoglobin falls to a low level, say 20 per cent. If this plan be followed life may be prolonged in some cases at least, as was doubtless true of my own case recorded in the table submitted, as well as the one reported by Dr. Bernheim and others to be found in the literature.

REPORT OF A CASE OF RUPTURE OF AN AORTIC ANEURYSM INTO THE LEFT INNOMINATE VEIN

By JAMES B. HERRICK, M.D.,
CHICAGO.

This case is reported simply in order to place on record another instance of rupture of an aneurysm of the aorta into the superior vena cava. I speak of rupture into the superior vena cava, though actually the rupture was into the left innominate vein, less than 1 cm. from the cava, the opening of communication being 1.5 cm. in diameter. The autopsy (Dr. B. A. Raulston) further showed marked old and active aortitis, typically luetic. The aneurysm had its origin 4 cm. above the aortic valves, the rounded sac, some 7 cm. in diameter, projecting in such a way as to produce a pressure constriction of the superior vena cava, especially marked close to the heart where it would clearly almost completely shut off circulation in the cava and block the azygos vein. The innominate and azygos veins were "hugely distended."

The diagnosis made after an examination of the patient, who came under my care in the Presbyterian Hospital January 12, 1919, was aortic aneurysm, with rupture into the superior vena cava. While I had never before seen a case of this sort, I remembered having heard Dr. Stengel make a report of one before this Association in 1900. On reading Dr. Stengel's[1] article one was referred to the fuller discussion of the subject by Pepper and Griffith[2] in their paper of 1890, also presented to this Association. In 1906, also, Fussell[3] had reported an additional case as had Cary.[4] A study of

[1] Tr. Assn. Am. Phys., 1900, xv.
[2] Ibid., 1890, v.
[3] Ibid., 1906, xvi.
[4] Ibid.

these reports, and particularly of the comprehensive digest of the topic by Pepper and Griffith, left little doubt that my case was of this nature.

Epitomized, as was done by Pepper and Griffith, the diagnosis rests on the following facts:

1. *Evidence from the History and Physical Examination*—including the tests for syphilis and the examination by the roentgen ray, both made available since the time of the Pepper communication—that an aneurysm exists in the thorax.

2. *The Sudden Onset of Symptoms attending the Rupture.* Other pressure causes may lead to edema and cyanosis; the aneurysm itself may have produced these results. But with the rupture there is nearly always a recognition by the patient, as in my case, of a sudden giving way of something in the chest, a rapid increase in the swelling, cyanosis, dyspnea, etc.

3. "*Cyanosis, Edema, Coldness and Distention of the Veins of the Upper Part of the Body, with other Evidences of Obstruction to the Circulation of the Blood in the Tributaries of the Superior Cava.*" If there is no obstruction below the point of entrance of the azygos vein, edema of the chest wall will be lacking; there would also be less likelihood of marked hydrothorax. The degree of cyanosis and dyspnea has varied in the cases reported. In mine it was extreme.

4. *A Murmur Heard toward the Base of the Heart.* This is usually continuous, with a ventricular systolic crescendo. The diastolic portion of the murmur is due to the current during arterial systole. In some cases a murmur only with the systole of the ventricle has been described. Evidently the type cannot be regarded as fixed, for the condition of the aortic valves, the extent of roughness of the aortic lining, the degree of elasticity of the arterial wall and the bruit in the aneurysmal sac must differ and contribute varying factors to the murmur. The most suggestive feature seems to be the continuousness of the murmur. "Like that heard in the enlarged vessels of a thyroid gland"—"a murmur characteristic of a communication between an artery and a vein." The murmur in my case resembled those which I have sometimes heard in cases of patent ductus Botalli.

The history was obtained with difficulty because the effort of

talking increased to an alarming extent the cough and dyspnea; besides, the patient was extremely irritable and at times delirious. He was a physician, aged thirty-three years. For six months he had suffered from pains in the chest which at times went out into the right arm. He admitted that he had "aortic disease," but whether by this he meant valvular disease or aneurysm was not clear. He denied syphilis, though the Wassermann test made a few days later was strongly positive (++++).

On the evening of December 9, 1918, he returned late to his office. As he was ascending the stairs he experienced a feeling as of something giving way in his chest; his neck and face felt flushed and full. The sense of choking and pressure was so urgent that as he entered the office he violently tore open his collar and the neckband of his shirt. While trying to turn on the electric light he lost consciousness. How long he lay in a swoon on the floor was not known; he thought about twenty minutes. After regaining his senses he turned on the light, looked in the mirror and saw that his face and neck were greatly swollen and "almost black in color." Breathing was difficult. He gave himself a hypodermic dose of some digitalis preparation and later summoned aid by telephone.

The history of the next five weeks is lacking in details; however, these are not essential to the story. As gathered from the patient and his wife there was most distressing dyspnea, much of the time amounting to orthopnea. Stormy spells of cough, with strangling and choking sensations and extreme cyanosis, seemed at times to threaten immediate death. The swelling of the face, neck and upper part of the body had been a striking feature of his illness, being noted almost from the first. There had been great difficulty in securing sleep even with the help of opiates. He had taken but a small amount of food, claiming that he had no appetite and that food distressed him. The thermometer had shown no rise in temperature. He had grown very weak, was irritable, unreasonable and at times somewhat delirious.

The picture presented, as I saw this patient for the first time five weeks after his accident, was one of which I have never seen the duplicate. The neck and face as well as the wall of the chest were swollen as in the anasarca of chronic parenchymatous nephritis;

the injected, bulging eyeballs could be seen through the narrow slits left between the swollen lids. But instead of the pasty pallor of the nephritic facies there was a purplish, almost black color, such as is seen only in the most extreme degrees of cyanosis. The visible veins were distended and tortuous. But no feature was more remarkable than the sharp contrast between the bloated, dark, upper half of the body and the pale, emaciated lower portion. The legs were the spindle legs of one in the terminal stages of a wasting disease, with no swelling and no pitting on pressure. There was no sign of free fluid in the scrotal sac or in the abdominal cavity. The liver was just palpable. The abdominal wall itself was not edematous except slightly so above the umbilical level. The line of separation between the non-swollen pale, flaccid abdominal wall and the swollen, purplish chest wall whose skin and subcutaneous tissue felt hard and brawny, pitting only on quite firm pressure, was almost as clear-cut as is the line of demarcation in a case of gangrene, being distinctly marked close to the costal margins.

Cardiac outlines were difficult to determine because of the thick, edematous chest wall, but the heart was evidently located somewhat to the left. And it was plain that there was an increased area of dulness at the base of the heart and over the manubrium. Here also could be very clearly heard the murmur already described, which is referred to in the history sheet as follows: "A systolic murmur, which lasts into diastole, is heard over the precordium in front and the interscapular region behind. At the aortic cartilage the murmur is particularly distinct and most intense. Here it is continuous, soft, blowing, somewhat humming in character. It is accentuated with the ventricular systole, so that at such times it becomes a loud, slightly roughened blow." There were numerous rales, both moist and dry, over the lungs, particularly behind. At the bases was dulness with some obscuring of breath sounds as from pleural fluid.

Until his death, eight days after I first saw him, there was no change for the better, rather a gradual loss in every respect. Breathing grew more and more difficult; cough was very annoying; there developed a dysphagia of marked degree; sleep was possible only by the help of drugs; food was taken in limited quantities. There

was no fever except one rise to 100° on January 15. Only occasionally was a trace of albumin found in the urine. A roentgenogram showed a shadow as from an aneurysm of the first or transverse portion of the aorta. The Wassermann test was strongly positive. The patient's mind was never quite clear, and much of the time was distinctly awry. He was irritable, unreasonable, often threatened to take his life. He gradually lost in strength, had spells of alarming cardiac weakness and finally lapsed into a condition of semistupor, from which he never fully rallied, dying January 20, 1919, at 2 o'clock in the morning.

Extended comment on this case is unnecessary, especially before this Association, to which several other similar cases have been reported and before which Pepper and Griffith presented their very complete study of the subject. The case is quite classic in its conformity to the condition as portrayed by these writers. While perforation of the aneurysm was not, strictly speaking, into the vena cava, it was so close to it—less than one-third inch—that in all essentials the case may be considered under that head.

While these typical cases permit of diagnosis if one carefully regards the history and physical findings, one may understand how variations in the size of the aneurysm, in the point of pressure on the cava, in the degree of obstruction produced and in the size of the ruptural opening may cause variations from the type, thus rendering diagnosis more difficult. Such differences in the anatomical lesion will explain the varying degrees of cyanosis and dyspnea, the absence of edema from the chest wall—azygos open—etc., in the cases as described by different writers.

Also one may understand how a mediastinal tumor might cause cyanosis, difficulty in breathing and swallowing, together with edema and venous engorgement of the upper part of the body; or how an aneurysm without rupture might lead to these symptoms. And the resemblance to the condition under consideration might be still more striking if valvular or aneurysmal murmurs or murmurs produced by pressure on vascular trunks were present. Diagnosis must at times be very perplexing. These difficulties are illustrated by a case reported by Sailer,[1] in which there was perforation of the

[1] Tr. Coll. Phys. Philadelphia, 1908, 3d S., xxx, 33.

aneurysm into the superior cava, though there was no clinical evidence of venous obstruction. On the other hand, Fussell[1] refers to a case in which sudden symptoms suggested perforation, yet none was found postmortem.

There is little that can be done for these patients except in a palliative way. Bleeding has been of only temporary benefit. Rest with the use of drugs to lessen distressing symptoms, such as cough, pain, sleeplessness, may tend to prolong life. Death may occur in a very short time after the accident, or it may be postponed many weeks or even months. One reported case is regarded as an instance of recovery.[2]

Fortunately the accident is rare. Pepper and Griffith, in 1890, found but 29 cases in the literature. Sixteen years later Fussell was able to add 7. The case here recorded, with 6 others found in the literature since 1906, makes a list of 43.[3]

[1] Tr. Coll. Phys. Philadelphia, 1908, 3d S., xxx, 34.

[2] Damaschino and Lavin: La France Médicale, 1882, i, 805.

[3] Cases recorded since 1906: Jos. Sailer: Tr. Coll. Phys., Philadelphia, 1908, 3d S., xxx, 33. O. H. Petty: Proc. Path. Soc., Philadelphia, 1914, xvi, 47; also Jour. Am. Med. Assn., 1913, lxi, 1810. W. G. McCallum: Proc. New York Path. Soc., 1915, N. S., xv, 27. J. L. Roberts: Liverpool Med.-Chir. Jour., 1910, xxx, 96. Paul Woolley: Am. Jour. Syph., St. Louis, 1917, i, 426. Laurence Humphry: British Med. Jour., 1910, ii, 1046. Jas. B. Herrick: Case here reported.

ASYNCHRONISM OF THE RESPIRATORY MOVEMENTS IN LOBAR PNEUMONIA

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(ABSTRACT)

Asynchronism of the respiratory movements in disease has been referred to only twice in the literature. It is characterized by a separation of the moment of contraction of the diaphragm and intercostal muscles by a definite, though variable, time interval. As far as my observations go the diaphragm contracts first, the abdominal wall is forced out, and then after varying intervals the contractions of the intercostals follow. Careful attention may be necessary to detect the lag in the movement of the thorax. Often the lowermost intercostals are the first to contract, and the movement of the thorax spreads in a wave from below upward. In the fully developed type of asynchronism the diaphragm has reached the expiratory phase before the contractions of the intercostals set in, and the abdomen and chest rise and fall alternately—"see-saw" best describes the impression conveyed. A slight delay in the contractions of the intercostal muscles has been observed in a variety of conditions, but in the author's experience the fully developed type of breathing has occurred only in lobar pneumonia.

Asynchronous breathing possesses particular interest from two standpoints: (1) its cause, and (2) its prognostic significance.

1. Cause: The cause of asynchronous breathing probably lies in unequal depression of different parts of the central nervous mechanism, that is, of different portions of the formatio reticularis, or of the formatio reticularis and the subsidiary centers in the gray matter of the cord.

2. Prognostic Significance: The completely developed form of asynchronous breathing has been observed only in patients who were desperately ill with lobar pneumonia. Without having kept an actual record, the author can recall only a few patients exhibiting the phenomenon who recovered. It usually develops late in the disease, but may appear within the first day or two, and give the first intimation of the gravity of the case. After many years the author has come to regard asynchronism as a sign of gravest import. While patients who develop it usually die, it does not occur in all fatal cases.

TWO CASES OF GONOCOCCAL PERITONITIS IN YOUNG GIRLS UNDER PUBERTY[1]

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The wording of the primary paper was: "Two cases of gonococcal peritonitis in young girls under puberty: one simulating appendicitis; operation." It was read before the Association of American Physicians and published in abstract in the *Transactions*, 1903, vol. xviii. It was also published in full in the *Archives of Pediatrics*, 1903, xx, 1910.

At the time there was discussion as to whether these girls suffering from infection of a virulent strain of gonococcus would not be made sterile from adhesive inflammation. After watching and waiting for sixteen years the question is answered.

Briefly the history was as follows: Gonococcal peritonitis, virulent strain, contracted from an adult member of the family. The onset was exceedingly abrupt, pain intense in the abdomen, marked tenderness, severe pain on micturation, localized pain and tenderness in the right iliac fossa, moderate abdominal distention, ghastly pallor, profound prostration, extreme relaxation, temperature 104½°. The adjectives are st ong ut not too strong: the onset can best be described by the rhetorical figure—"a bolt from the sky."

The first symptom was vomiting (once); within six hours she was in the care of Dr. George Woolsey, undergoing an exploratory operation for appendicitis (Presbyterian Hospital).

It is not often that one sees the lesion of peritonitis at this early

[1] Sixteen years later, answer to the question: "Can these girls bear children?" Original paper published in the Transactions of the Association of American Physicians, 1903.

stage, and the lesson may serve for others than those present. Suffice it here to refer to the original paper and repeat that the one striking appearance was that of intense injection of the vessels, described as an "arborescent injection": the whole peritoneum, especially about the cecum, was blood red. A little straw-colored serum was present in the peritoneum. The appendix, ovaries and tubes seemed injected like the rest of the surface. According to the authorities of that time it was pronounced a cellular inflammation: from subsequent history it would seem to have been of the non-adhesive variety. Recovery was prompt from operation and disease.

The answer to the first question is that: The child operated on bore her first child in the present year 1919. The second case died of diabetes.

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